Optical coherence tomography for the diagnosis, monitoring and guiding of treatment for neovascular age-related macular degeneration

Optical coherence tomography for the diagnosis, monitoring, and guiding of treatment for neovascular age-related macular degeneration: a systematic review and economic evaluation

Report commissioned by: NIHR HTA Programme

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Date completed: 30th January 2014

Version 1

Source of funding

This report was commissioned by the NIHR HTA Programme as project number 10/57/22.

Declared competing interests of authors

AL has received honoraria from Bayer, Novartis and Alcon and his institution has received educational grants from Novartis Pharmaceuticals. WA has received personal fees from Alcon, Alimera, Allergan, Bayer, Novartis and Thrombogenics, grants from Allergan and Novartis, non-financial support from CentreVue SpA and Novartis, and other support from Pfizer. There are no other competing interests.

All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare (1) no financial support for the submitted work from anyone other than their employer; (2) no financial relationships with commercial entities that might have an interest in the submitted work; (3) no spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; and (4) no non-financial interests that may be relevant to the submitted work.

Acknowledgements

We thank David Findlay Clark (service user with the condition), Graham Findlay (Chief Executive, North East Sensory Services) and Helen Jackman (Chief Executive, Macular Society) for providing valuable consumer insight and advice, and for commenting on the plain English summary, and Malcolm McPherson (Community Optometrist) for providing a community optometrist perspective, through their participation as members of the study's Project Advisory Group; Usha Chakravarthy, Chris Rogers and colleagues for providing data from the IVAN trial; Mari Imamura and Xueli Jia for translating non-English language papers; and Lara Kemp for secretarial support.

The economic model developed for the analysis was informed by an existing economic model developed by the Southampton Health Technology Assessments Centre (SHTAC), University of Southampton, UK. The intellectual property rights associated with the SHTAC economic model are owned by the University of Southampton (UK) – all rights reserved. We thank Andrew Clegg and Jeremy Jones for providing access to the SHTAC age-related macular degeneration economic evaluation model (see http://www.southampton.ac.uk/shtac/research/published/eyediseases.page?).

This report was commissioned by the NIHR HTA Programme as project number 10/57/22. The Health Services Research Unit and Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen are core-funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorates. The views and opinions expressed are those of the authors and do not necessarily reflect those of the funders.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Mowatt G, Hernández R, Castillo M, Lois N, Elders A, Fraser C, Aremu O, Amoaku W, Burr J, Lotery A, Ramsay C, Azuara-Blanco A. Optical coherence tomography for the diagnosis, monitoring, and guiding of treatment for neovascular age-related macular degeneration: a systematic review and economic evaluation. Health Services Research Unit, Institute of Applied Health Sciences, University of Aberdeen, 2013.

Contributions of authors

Graham Mowatt (co-principal investigator, Senior Research Fellow) coordinated the study and wrote the decision problem, methods and assessment of diagnostic and monitoring studies chapters and sections of the scientific summary, discussion and conclusions chapters. Augusto Azuara-Blanco (co-principal investigator, Professor of Ophthalmology) jointly coordinated the study with Graham Mowatt, wrote the background and factors relevant to the NHS and other parties chapters, sections of the scientific summary, discussion and conclusions chapters, and was responsible for the final editing. Mayret Castillo (Research Assistant) led the day-to-day running of the study and reviewed the evidence on test performance with assistance from Graham Mowatt and Augusto Azuara-Blanco. Rodolfo Hernández (Research Fellow) conducted the economic evaluation and wrote the cost-effectiveness chapter and sections of the scientific summary, discussion and conclusions chapters. Noemi Lois (Professor of Ophthalmology) wrote sections of the background and factors relevant to the NHS and other parties chapters. Olatunde Aremu (Research Fellow) was involved with the initial development of the economic model (model conceptualisation), with supervision from Rodolfo Hernández. Cynthia Fraser (Information Specialist) developed and ran the search strategies, managed the reference database and formatted references. Andrew Elders (Statistician) provided statistical support. Noemi Lois, Augusto-Azuara-Blanco, Jennifer Burr (Reader), Winfried Amoaku (Clinical Associate Professor and Reader in Ophthalmology and Visual Sciences) and Andrew Lotery (Professor of Ophthalmology) provided expert advice on clinical aspects of the study.

Craig Ramsay (Health Care Assessment Programme Director) and Jennifer Burr provided advice on methodological aspects of the study. All authors commented on drafts of the report.

ABSTRACT

Background

Age-related macular degeneration (AMD) is the commonest cause of sight impairment in the UK. In neovascular AMD (nAMD), vision worsens rapidly (over weeks) due to abnormal blood vessels developing that leak fluid and blood at the macula.

Objectives

To determine the optimal role of optical coherence tomography (OCT) in diagnosing people newly presenting with suspected nAMD and monitoring those previously diagnosed with the disease.

Data sources

Databases searched: MEDLINE (1946 to March 2013), MEDLINE In Process (March 2013), EMBASE (1988 to March 2013), Biosis (1995 to March 2013), SCI (1995 to March 2013), the Cochrane Library (Issue 2 2013), DARE (March 2013), MEDION (March 2013), HTA database (March 2013).

Methods

Types of studies: direct/indirect studies reporting diagnostic outcomes. Index test: time domain (TD) or spectral domain (SD) OCT. Comparators: clinical evaluation, visual acuity, Amsler chart, colour fundus photographs, infra-red reflectance, red-free images/blue reflectance, fundus autofluorescence imaging, indocyanine green angiography, preferential hyperacuity perimetry, microperimetry. Reference standard: fundus fluorescein angiography (FFA). Risk of bias was assessed using QUADAS-2. Meta-analysis models were fitted using hierarchical summary receiver operating characteristic (HSROC) curves.

A Markov model was developed (65 year old cohort, nAMD prevalence 70%), with nine strategies for diagnosis and/or monitoring, and cost-utility analysis conducted. NHS and Personal Social Services perspective was adopted. Costs (2011/12 prices) and quality-adjusted life years (QALYs) were discounted (3.5%). Deterministic and probabilistic sensitivity analyses were performed.

Results

In pooled estimates of diagnostic studies (all TD-OCT), sensitivity and specificity (95% CI) was 88% (46% to 98%), and 78% (64% to 885%), respectively. For monitoring, the pooled

sensitivity and specificity (95% CI) was 85% (72% to 93%) and 48% (30% to 67%), respectively. for TD-OCT and SD-OCT combined

The FFA for diagnosis and nurse/technician-led monitoring strategy had the lowest cost (£39,769; QALYs 10.473) and dominated all others except FFA for diagnosis and ophthalmologist-led monitoring (£44,649; QALYs 10.575; ICER £47,768). The least costly strategy had a 46.4% probability of being cost-effective at £30,000 willingness to pay threshold.

Limitations

Very few studies provided sufficient information for inclusion in meta-analyses. Only a few studies reported other tests; for some tests no studies were identified. The modelling was hampered by a lack of data on the diagnostic accuracy of strategies involving several tests.

Conclusions

Based on a small body of evidence of variable quality, OCT had high sensitivity and moderate specificity for diagnosis, and relatively high sensitivity but low specificity for monitoring. Strategies involving OCT alone for diagnosis and/or monitoring were unlikely to be cost-effective. Further research is required on (i) the performance of SD-OCT compared with FFA, especially for monitoring but also for diagnosis (ii) the performance of strategies involving combinations/sequences of tests, for diagnosis and monitoring, (iii) the likelihood of active and inactive nAMD becoming inactive or active, respectively, and (iv) assessment of treatment-associated utility weights (e.g. decrements), through a preference based study.

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PLAIN ENGLISH SUMMARY

In wet age-related macular degeneration (AMD), abnormal blood vessels develop that leak fluid and blood in the back of the eye, causing central vision to worsen rapidly (over weeks). Optical coherence tomography (OCT) is a non-invasive imaging test, widely used in the NHS, that can detect wet AMD. The more recent spectral domain OCT (SD-OCT) contains improvements over time domain OCT. OCT is usually used along with other tests, such as visual acuity. This review assessed the evidence for the usefulness of OCT in diagnosing people newly presenting with suspected wet AMD, and in determining disease activity during regular monitoring visits for those previously diagnosed with the condition. The date of the last literature searches was March 2013. Twenty-two diagnostic and eight monitoring studies were included. The evidence suggested that, for diagnosis, OCT had high sensitivity (very few people with wet AMD would be wrongly diagnosed as not having it) and moderate specificity (around one quarter of those without wet AMD would be wrongly diagnosed as having it). For monitoring, OCT also had high sensitivity but low specificity (half of those without active disease would be wrongly diagnosed as having it). Therefore, although OCT is a sensitive test and would detect most people with wet AMD, if used as the only test to guide treatment then, potentially, a considerable number of people with inactive disease would receive treatment. However, these results should be interpreted with caution due to the small number of studies identified, and their variable quality.

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1 GLOSSARY AND LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

GLOSSARY

Case-control study	This type of study compares a group of people who have the disease and a group who do not have it
Choroidal neovascularisation	New blood vessels originating from the choroid. The choroid is a thin layer of connective tissue that lies between the retina and the sclera and supplies blood to the outer layers of the retina
Diagnostic odds ratio	The ratio of the odds of testing positive in those with the disease relative to the odds of testing positive in those without the disease
Direct head-to-head study	A study in which people receive both index and comparator tests and they are therefore evaluated in the same participants
False negative/true negative/false positive/ true positive	In terms of diagnostic accuracy, indicators of index test results as compared to the reference standard: negative index test, positive reference standard/negative index test, negative reference standard/positive index test, negative reference standard/positive index test, positive reference standard
Fundus fluorescein angiography	An invasive imaging test that examines the circulation of the retina and choroid. A fluorescein dye is injected into a vein in the arm and a specialised camera photographs the dye as it passes through the blood vessels in the eye
Index test	The diagnostic test which is being evaluated
Likelihood ratio	A description of how many times more likely it is that a person with the disease will receive a particular test result than a person without the disease
Macula	The central part of the retina containing the xanthophyll pigment and two or more layers of ganglion cells. Damage to

	the centre of the macula, the so-called fovea, often results in loss of central vision
Meta-analysis	The quantitative pooling of data from two or more studies
Negative predictive value	The proportion of those with negative test results who do not have the disease
Neovascular age-related macular degeneration	In neovascular or 'wet' age-related macular degeneration, abnormal blood vessels grow into the macula and leak blood or fluid, leading to scarring of the macula and rapid loss of central vision
Optical coherence tomography	A non-invasive imaging technology used to obtain high resolution cross-sectional images of the retina
Positive predictive value	The proportion of those with positive test results who actually have the disease
Randomised controlled trial (RCT)	A study in which people are randomly allocated to receive – or not receive – a particular treatment or intervention. This is said to be the best study type to determine effectiveness of a treatment
Reference standard	The best available test for establishing the presence or absence of the disease
Retina	The light-sensitive layer of tissue located in the back of the eye. The retina receives images via the eye's lens, converts them to electric signals and transmits them to the brain
Sensitivity	The proportion of those who actually have the disease and who are correctly identified with positive test results
Specificity	The proportion of those who actually do not have the disease and who are correctly identified with negative test results
Visual acuity	Sharpness of vision, which is tested by identifying characters on a chart from a set distance. Normal visual acuity is usually referred to as 20/20 vision, meaning the detail that a person with normal eyesight would see from 20 feet away
Visual impairment	≤ 6/60 to > 3/60, severe visual impairment;

	≤ 3/60, profound visual impairment/blindness

LIST OF ABBREVIATIONS

AAO	American Academy of Ophthalmology
AMD	Age-related macular degeneration
anti-VEGF	Anti-vascular endothelial growth factor
ARVO	Association for Research in Vision and Ophthalmology
BIOSIS	Bioscience Information Services
BNF	British National Formulary
CATT	Comparison of Age-related Macular Degeneration Treatments Trials
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CIs	Confidence intervals
CNV	Choroidal neovascularisation
CNVM	Choroidal neovascular membrane
DARE	Database of Abstracts of Reviews of Effects
DOR	Diagnostic odds ratio
DS-ICGA	Digital subtraction indocyanine green angiography
ETDRS	Early Treatment Diabetic Retinopathy Study
EVER	European Association for Vision and Eye Research
FAF	Fundus autofluorescence
FFA	Fundus fluorescein angiography
FN	False negative
FP	False positive
FPED	Fibrovascular pigment epithelial detachment
GPs	General Practitioners
HCHS	Hospital and Community Health Service
HSROC	Hierarchical summary receiver operating characteristic
ICER	Incremental cost-effectiveness ratio
ICG	Indocyanine green
ICGA	Indocyanine green angiography
ICTRP	International Clinical Trials Registry Platform
IPCV	Idiopathic polypoidal choroidal vasculopathy
IR	Infa-red reflectance
IVAN	A randomised controlled trial of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation
LLIO	Late leakage of indeterminate origin

LR	Likelihood ratio
nAMD	Neovascular age-related macular degeneration
NHS	National Health Service
NIA	Near-infrared autofluorescence
NICE	National Institute for Health and Care Excellence
NIR	Near infrared fundus reflectance
OCT	Optical coherence tomography
Oph	Ophthalmologist
PDT	Photodynamic therapy
PED	Pigment epithelial detachment
PHP	Preferential hyperacuity perimetry
QALY	Quality-adjusted life year
QUADAS-2	Quality assessment of diagnostic accuracy studies, version 2
RAP	Retinal angiomatous proliferation
RCO	Royal College of Ophthalmologists
RCT	Randomised controlled trial
RF	Red-free images
RPE	Retinal pigment epithelium
RR	Relative risk
SCI	Science Citation Index
SD-OCT	Spectral domain optical coherence tomography
SLB	Slit-lamp biomicroscopy
SLO	Scanning laser ophthalmoscope
SROC	Summary receiver operating characteristic
TD-OCT	Time domain optical coherence tomography
Tech	Technician
TN	True negative
TP	True positive
VA	Visual acuity
VEGF	Vascular endothelial growth factor
WMD	Weighted mean difference

2 SCIENTIFIC SUMMARY

Background

Age-related macular degeneration (AMD) is the commonest cause of sight impairment in the UK. In neovascular AMD (nAMD), vision worsens rapidly (over weeks) due to abnormal blood vessels developing that leak fluid and blood at the macula. For patients with nAMD it is common practice to initiate treatment with three consecutive (monthly) injections of anti-vascular endothelial growth factor (anti-VEGF) therapy, and then the patient is reassessed to evaluate whether or not the disease is active or inactive. Many patients require monthly monitoring and treatment over a period of several years. Fundus fluorescein angiography (FFA), an invasive test, is considered the reference standard for detecting nAMD at initial presentation and it is also used for detecting recurrent activity at some monitoring visits. Optical coherence tomography (OCT) is a non-invasive test that can be used for detecting nAMD at initial presentation and is often used as the only imaging test for detecting recurrent activity during monitoring visits. The more recently introduced spectral domain OCT (SD-OCT) incorporates a number of improvements over time domain OCT (TD-OCT).

Objectives

This review aims to determine the optimal role of OCT in (i) the diagnosis of people newly presenting with suspected neovascular AMD and (ii) in monitoring those previously diagnosed with the disease.

Methods

Electronic databases searched included MEDLINE, MEDLINE In-Process, EMBASE, Bioscience Information Service (BIOSIS), Science Citation Index (SCI), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Medion, Health Technology Assessment database, PsycINFO, ASSIA, conference abstracts from the American Academy of Ophthalmology (AAO), the Association for Research in Vision and Ophthalmology (ARVO), the European Association for Vision and Eye Research (EVER) and current research registers. Searches were carried out from 1995 to March 2013 other than for conference abstracts (2009 to November 2012).

Types of studies considered were direct or indirect comparisons reporting diagnostic outcomes. The population was people with newly suspected nAMD or those previously diagnosed with the disease and under surveillance monitoring. The index test was TD-OCT or SD-OCT and comparator tests considered were clinical evaluation, visual acuity, Amsler chart, colour fundus

photographs, infra-red reflectance, red-free images or blue reflectance, fundus autofluorescence imaging (FAF), indocyanine green angiography (ICGA), preferential hyperacuity perimetry (PHP) and microperimetry. The reference standard was FFA.

Two reviewers independently screened the titles and abstracts of all reports identified by the search strategy and full-text papers were obtained for assessment. Data extraction was undertaken by one reviewer and checked by a second. Two reviewers independently assessed the risk of bias of the studies using the QUADAS-2 instrument.

The results of the individual studies were tabulated and sensitivity, specificity and their 95% confidence intervals (CIs) presented for each test or combination of tests. The presence of heterogeneity was assessed by visual examination of forest plots of sensitivity and specificity. Summary receiver operating characteristic (SROC) curves were derived. Meta-analysis models were fitted using hierarchical SROC (HSROC) curves. Summary sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios were reported as median and 95% CI.

An economic model was developed to assess the cost-effectiveness of different strategies for diagnosis and monitoring of individuals with nAMD. Three strategies were selected for the diagnostic stage and three for the monitoring stage, giving a total of nine diagnosis-monitoring combinations.

Diagnostic strategies

a) Stereoscopic FFA interpreted by an ophthalmologist. If positive (i.e. presence of nAMD), treat and monitor; if negative, discharge.
b) SD-OCT alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge.
c) Visual Acuity (VA) and SD-OCT and slit-lamp biomicroscopy (SLB) in all patients, performed/interpreted by an ophthalmologist. If positive or unclear, arrange for a FFA. If negative, discharge. This is the diagnostic strategy that best reflects standard practice.

Monitoring strategies

a) SD-OCT alone (interpreted by an ophthalmologist). If positive, treat. If negative or unclear, review in one month's time.
b) VA, SLB and SD-OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in one month's time. If unclear, then the ophthalmologist will arrange for a FFA. This is the monitoring strategy that best reflects standard practice.

c) VA and SD-OCT interpreted by a technician or nurse. If negative, review in one month's time. If positive or unclear, referral to an ophthalmologist for assessment (e.g. SLB and ophthalmologist interpretation of VA and SD-OCT test results). If positive, treat; if negative, review in one month's time; if unclear, arrange for a FFA.

The model was run for a cohort of 65 year old men for a lifetime time horizon. A one-month cycle length was defined. Costs were expressed in 2011-2012 pounds sterling and effectiveness in quality-adjusted life years (QALYs). Costs and QALYs were discounted at 3.5%. Cost-effectiveness analysis results were reported using incremental cost-effectiveness ratios (ICERs).

Uncertainty was explored by conducting one-way sensitivity analyses, scenario analysis and probabilistic sensitivity analysis. One-way sensitivity analyses were conducted on test sensitivity and specificity for diagnosis, the probability of ophthalmologist diagnosis or monitoring having unclear results, test sensitivity and specificity for monitoring, the probability of the nurse or technician assessment being unclear, and unit costs for OCT, FFA and ranibizumab treatment.

In addition, three scenario analyses were tested. All of these incorporated data favouring OCT (e.g. scenario 1 included the 95% CI upper limit for OCT sensitivity and specificity for diagnosis and monitoring, with £20.90 and £139 unit costs for OCT and FFA, respectively). Scenario 2 assumed a cost per treatment injection of £50 instead of £742, and scenario 3 explored the effect of monitoring patients with OCT only, within the community, with referral to secondary care only for treatment.

Results

Number and quality of studies

Twenty-two diagnostic studies (20 full-text, two abstracts) enrolling 2,124 people and eight (full-text) monitoring studies enrolling 463 people were included. Only full-text studies were assessed for risk of bias. For both the diagnostic and monitoring studies, the domains in which the greatest number of studies were judged to be at high risk of bias were the patient selection domain (55%, 11/20; 25%, 2/8) and flow and timing domain (40%, 8/20; 25%, 2/8).

Summary of benefits and risks

Diagnostic studies

In a meta-analysis of diagnostic studies (four TD-OCT studies) sensitivity and specificity (95% CI) was 88% (46% to 98%) and 78% (64% to 88%) respectively.

In descriptive analyses, across the studies reporting other tests, median sensitivity was high for ICGA (93.2%, range 84.6% to 100%; four studies) and FAF (93.3%; one study), followed by PHP (81.5%, range 50.0% to 84.8%; three studies), colour fundus photography (70.0%; one study) and lowest for Amsler Grid (41.7%; one study). Specificity was highest for colour fundus photography (95%; one study), followed by PHP (84.6% and 87.7%; two studies), and was low for FAF (37.1%; one study) and ICGA (36.8%; one study).

Monitoring studies

In a meta-analysis of monitoring studies (three TD-OCT, two SD-OCT studies), sensitivity and specificity (95% CI) was 85% (72% to 93%) and 48% (30% to 67%) respectively. For TD-OCT, sensitivity and specificity was 70% (56% to 80%) and 65% (48% to 79%) respectively. It was not possible to calculate pooled estimates using HSROC methodology for the two SD-OCT monitoring studies due to insufficient data. These studies reported high sensitivity of 94% and 90% but low specificity of 27% and 47%.

In the one monitoring study reporting ICGA, sensitivity of 75.9% and specificity of 88.0% was reported for detecting nAMD activity.

Summary of cost-effectiveness

The strategy that based its diagnostic decision on the results of FFA only, combined with VA and OCT interpreted together by a nurse or technician as a first monitoring step ('FFA&Nurse'), had the lowest total expected cost. This strategy dominated (i.e. lower total cost and higher QALYs) all others apart from one. Diagnosis based on FFA only, followed by ophthalmologist-led monitoring (FFA&Ophthalmologist), had a higher total expected cost and also produced higher total expected QALYs but at a cost per additional QALY above £30,000. Moreover, the 'FFA&Nurse' strategy had a 46.5% probability of being cost-effective at a £30,000 threshold value of willingness to pay for an extra QALY. Strategies using OCT alone for diagnosis or monitoring were unlikely to be cost-effective. This result seemed to be driven by the SD-OCT low specificity that resulted in a high number of false positives.

Discussion

Strengths, limitations of the analyses and uncertainties

In terms of strengths, a systematic literature search was undertaken and non-English language studies were included. A HSROC model was applied, which takes account of the trade-off between true/false positives and models between-study heterogeneity. The evidence for diagnosis and monitoring was considered separately, as was the evidence for TD-OCT and SD-OCT. Regarding the economic model, multiple different pathways were developed and evaluated. In terms of limitations, very few studies provided sufficient information for inclusion in meta-analyses. Only a few studies meeting our inclusion criteria reported the performance of other diagnostic tests of interest; for some tests no studies were identified. The modelling was hampered by a lack of data on the diagnostic accuracy of strategies involving several tests (performed by ophthalmologists or other health professionals).

In terms of uncertainties, there was substantial disagreement between OCT and FFA specificity, especially for monitoring. As FFA was considered the reference standard it was not possible to assess whether OCT might have better sensitivity or specificity than FFA. It was unclear why the specificity was lower for SD-OCT compared with TD-OCT.

The model was based on one eye status and outcomes, as this is the approach most commonly used in this health area. The so named 'one eye models' can underestimate resources used due to a proportion of nAMD individuals having active nAMD in both eyes in one particular visit. In the current model, this would increase the cost for those strategies with a higher number of false positives (i.e. lower specificity) and therefore would be unlikely to modify the general conclusions of this report. In addition, the model did not consider effects on utility due to treatment injections and frequent monitoring. Anxiety in nAMD individuals was believed to occur at each monitoring visit mainly due to uncertainty of the underlying condition rather than the effects of treatment injections. Limited evidence was available on the probability of nAMD active individuals becoming inactive when under treatment or inactive nAMD individuals becoming active. Short time follow-up data were extrapolated to a lifetime time horizon.

Generalisability of the findings

From the populations evaluated in the primary studies, the results of this report are broadly generalisable to the NHS. One of the UK-based diagnostic studies evaluated a nurse-led, fast track screening clinic, which may not be representative of current UK practice. In addition 55% of the diagnostic and 25% of the monitoring studies were considered to be at risk of selection bias due to either pre-selection of participants and/or inappropriate exclusions.

Conclusions

Implications for service provision

In terms of OCT test performance, this review found that, based on a relatively small body of evidence of variable quality:

- For diagnosis of newly suspected nAMD, SD-OCT had high sensitivity (98%) and moderate specificity (71%) (meta-analysis).
- For monitoring of those previously diagnosed with nAMD, SD-OCT had high sensitivity (94%, 90%) but low specificity (27%, 47%) (two studies).
- For both diagnosis and monitoring, SD-OCT had higher sensitivity than TD-OCT but lower specificity.

The strategy that based its diagnostic decision on the results of FFA only, combined with a nurse or technician-led stepwise approach for monitoring, had the lowest expected total cost and a 47% probability of being cost-effective at a £30,000 threshold value of willingness to pay for an extra QALY. Strategies using OCT test results alone to make diagnosis and/or monitoring treatment decisions were unlikely to be a cost-effective use of resources.

There has already been a shift in the diagnostic and monitoring pathways for nAMD caused by the adoption of OCT. At the diagnostic stage OCT is currently used in addition to FFA (reference standard), while for monitoring it has virtually replaced FFA, which is only used in selected circumstances. The evidence suggests that using OCT as the only test for monitoring patients with nAMD and detecting activity would, potentially, result in a substantial proportion of patients receiving treatment unnecessarily.

The continuing rise in the ageing population, with increasing numbers of people being diagnosed with nAMD and moving on to monitoring for renewed disease activity, will continue to present challenges for ophthalmology departments to have sufficient capacity to provide timely testing, and treatment.

Suggested research priorities

- Regarding monitoring of nAMD, in current practice OCT is routinely used, while FFA is used only in particular scenarios. There is a substantial disagreement between OCT and FFA. There is a need to research that OCT (without FFA) is an acceptable way of detecting active nAMD and guiding treatment. As there is the theoretical possibility of OCT being better in some cases than the current reference standard, such studies might be designed to include a 'fair umpire' test, if available, to examine differences between OCT and FFA, or

be designed to incorporate sufficient follow-up to assess the consequences of the tests in terms of clinical effectiveness outcomes (e.g. visual acuity).

- Regarding diagnosis of nAMD, current practice consists of FFA (as reference standard) associated with OCT. Further research should be considered to establish the added value of OCT, and whether OCT (associated with slit-lamp biomicroscopy and visual acuity) can fully replace FFA. As above, such studies might be designed to include a 'fair umpire' test, or the evaluation of the consequences of the diagnostic intervention.
- Regarding the different phenotypes of nAMD, further evidence on the diagnostic performance of OCT according to phenotype of nAMD is required.
- For both diagnosis and monitoring of nAMD, prospective studies are required to assess the diagnostic accuracy and clinical effectiveness of strategies involving possible different combinations and sequences of tests (e.g. visual acuity, slit-lamp biomicroscopy, fundus autofluorescence imaging, OCT), including a comparison of their interpretation by ophthalmologists compared with other health professionals.
- To strengthen the evidence base used to develop the economic model, it would be important to explore the likelihood of active and inactive nAMD individuals becoming inactive or active, respectively. In addition, a preference based study to assess utility weights (e.g. decrements) associated with treatment and frequent monitoring is needed.
- Further research is needed to evaluate health status (utilities) in patients with nAMD, taking into consideration the visual function and spectrum of disease in both eyes and exploring the value added by inclusion of fellow eye information.

Prospero registration number: CRD42012001930

[Word count: 2400 words]

3 BACKGROUND

3.1 Description of health problem

3.1.1 Brief statement describing the health problem

Neovascular age-related macular degeneration (nAMD) causes severe visual loss and is the commonest cause of blindness in persons > 50 years old in the western world. In recent years, there have been significant advances in the clinical management of patients with nAMD. For example, there are now effective treatments, specifically anti-vascular endothelial growth factor (anti-VEGF), and novel diagnostic technologies, including both imaging and functional tests. Patients who are being treated for nAMD with anti-VEGF require frequent and long-term follow-up for treatment to be most effective.

The current reference standard for diagnosis of nAMD is fundus fluorescein angiography (FFA)[1] which may also be used to monitor the activity of the disease after treatment. However, FFA is time-consuming, invasive and requires expert interpretation. Optical coherence tomography (OCT) is now widely used for diagnosis and management of nAMD. OCT is non-invasive, safer and more straightforward to do and interpret than FFA. OCT may help clinicians to provide a more cost-effective service for people with nAMD by potentially replacing the current reference standard of FFA and helping to distinguish between those patients with active disease requiring treatment and those whose disease is not active at a particular point in time and who do not require treatment. OCT might also lead to efficiencies by allowing other categories of health professionals to become involved in the diagnosis and monitoring of patients.

3.1.2 Aetiology, pathology and prognosis

Neovascular AMD is a pathological process in which new blood vessels arising from the choroid breach the normal tissue barriers and come to lie within the subretinal pigment epithelium (RPE) and/or subretinal spaces. These new vessels, commonly referred to as choroidal neovascularisation (CNV) or choroidal neovascular membrane (CNVM), leak fluid, lipids and blood, elicit an inflammatory response and, as part of their natural history, undergo a scarring process, all of which has a deleterious effect on the visual cells of the retina (photoreceptors), leading to central loss of vision. Besides CNV, there are two other recognised phenotypes of nAMD (a) retinal angiomatous proliferation (RAP) in which vascular complex seems to arise *de novo* from the retinal circulation, or results from CNV anastomosing with the retinal circulation; and (b) intra-choroidal/subretinal pigment epithelium (RPE) aneurysmal dilatation(s) of the choroidal vasculature, known as idiopathic polypoidal choroidal

vasculopathy (IPCV).[2] These phenotypes may occur in isolation or be mixed with other phenotypes.[3]

The onset of nAMD results in progressive and unremitting loss of central vision in the affected eye, with rare exceptions in cases of IPCV in which spontaneous improvement may be observed. A number of studies have shown that extrafoveal CNV will grow towards the fovea. Once foveal involvement has occurred CNV will expand and involve ever-increasing areas of the macula. Thus the majority of eyes will experience acute visual loss, either moderate (defined as a doubling of the visual angle which equates to a three line worsening on the Early Treatment Diabetic Retinopathy Study [ETDRS] visual acuity chart) or severe (defined as a quadrupling of the visual angle and which equates to a six line worsening on the ETDRS visual acuity chart). However, some patients with a fellow eye with good vision will not notice any such changes despite the onset of neovascularisation.

Neovascular AMD is now treated with repeated intraocular injections of drugs designed to antagonise vascular endothelial growth factor (anti-VEGF). This will stabilise sight in most patients (~90%), and improves vision in a smaller group (~30%) during the first two years of treatment.[1] Long-term (beyond 3-4 years) outcomes from randomised clinical trials (RCTs) using anti-VEGF are, however, not available. These drugs are administered monthly (often with a mandated minimum of three injections for the first three months, and thereafter depending on whether active nAMD is present) as intraocular injections until the macula is rendered fluid free. When the disease becomes quiescent, treatment is stopped and patients are monitored for relapse, with treatment being restarted if needed, by monthly intraocular injections based on findings of visual acuity checks, clinical examination and OCT. FFA is typically used to confirm the diagnosis of nAMD prior to initiating anti-VEGF therapy, but it is used only in selected circumstances for monitoring activity of nAMD after treatment. Relapse of nAMD is unpredictable and can occur within weeks, months or even years after stopping treatment.

3.1.3 Epidemiology, incidence and prevalence

The prevalence of all forms of AMD (including neovascular and atrophic AMD), which affects more than 600,000 people in the UK, is expected to rise by a quarter to nearly 756,000 by 2020. The estimated number of individuals with nAMD in the UK for 2011 is 368,000 and will increase substantially due to the ageing population.[4-6] Estimates of incidence of nAMD in the UK suggest that there are between 13,000 and 37,000 new cases annually.[5] The NICE guidance on ranibizumab and pegaptanib for the treatment of age-related macular degeneration (issued 2008 and modified 2012) estimated that there were about 26,000 new cases of nAMD in the

UK each year.[7] Many of these individuals will require monthly monitoring and treatment for several years. Relevant risk factors include age, cigarette smoking, nutritional factors, cardiovascular diseases, and genetic markers, including genes regulating complement, lipid, angiogenic, and extracellular matrix pathways.

3.1.4 Impact of health problem

Significance for patients in terms of ill-health (burden of disease); significance for the NHS

AMD is the most common cause of blindness and partial sighted registration in the UK.[1] As the incidence of AMD increases with age, the burden of disease to the NHS and society is expected to increase with an ageing population. Furthermore, loss of vision contributes to a psychological ill-health (depression, emotional distress) and reduced quality of life.

Ophthalmology accounts for 10% (five million per year) of all outpatient attendances to the NHS, and age-related macular degeneration accounts for 15% of all ophthalmology outpatient attendances.[1] Loss of visual acuity is associated with a profound impairment of quality of life. Visual loss increases the risk of frequent falls. Depression and visual hallucinations (Charles Bonnet syndrome) are frequent accompaniments of severe central vision loss. Patients with Charles Bonnet syndrome (associated with visual loss) and their family members should be informed that visual symptoms are not unusual and are not a sign of psychosis or mental deterioration.

3.1.5 Measurement of disease

The spectrum of disease may be classified according to the reduction of visual acuity, e.g., mild, moderate, or severe. In addition to this spectrum of disease, during monitoring of patients undergoing treatment with anti-VEGF drugs, it is important to determine whether the disease is active or not. Disease activity is typically determined with imaging technologies, mainly FFA and OCT.

3.2 Current service provision

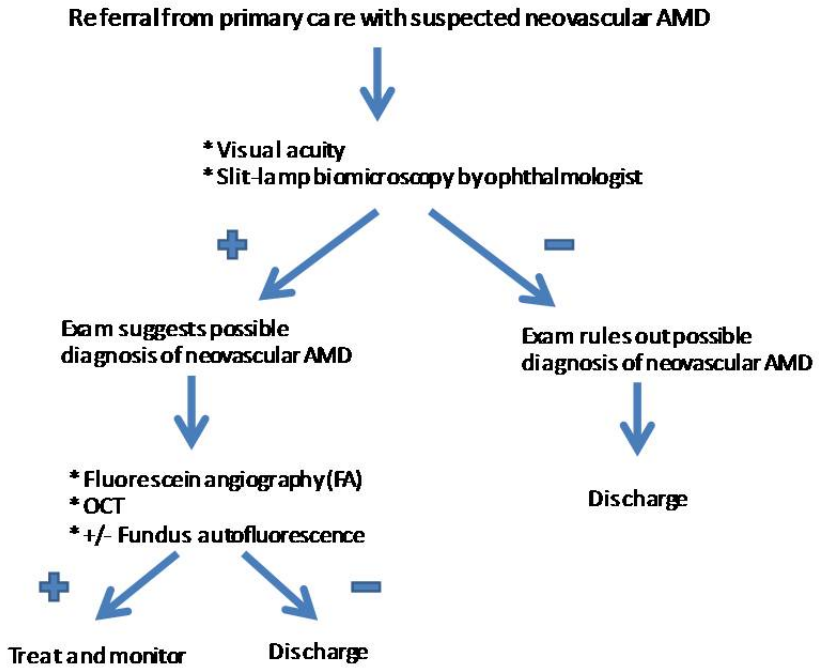
3.2.1 Management of disease

Diagnosis of nAMD and care pathway

Typically patients with possible AMD present to primary care (optometrists or GPs) with non-specific symptoms (such as reduced, blurred and distorted vision). Some patients do not report symptoms and are detected at routine eye examination. Clinical examination of the retina reveals typical changes associated with AMD such as drusen and irregularities in the appearance of the RPE, most commonly in both eyes. However the presence of a neovascular component may be difficult to detect clinically, especially early on in the course of its

development. The diagnostic pathway for nAMD and the management of patients with known disease include imaging technologies (Figure 1).

Figure 1 Current diagnostic pathway of nAMD



According to current guidelines from the Royal College of Ophthalmologists (RCO),[1] FFA interpreted by an ophthalmologist is the method of choice and reference standard test to diagnose nAMD. Occasionally, indocyanine green angiography is associated with FFA as part of the reference standard when particular phenotypes of nAMD are suspected, including RAP and IPCV (see above). FFA is an invasive and time-consuming procedure, entailing the injection of a dye into a peripheral vein by a nurse and a trained photographer to undertake the test (obtain the images of the CNV, RAP, IPCV lesions). In addition to FFA, current guidelines recommend using OCT at diagnosis. Due to recent developments in technology, it is possible that in some cases OCT might be superior to FFA in detecting nAMD (see below and Table 1).

Table 1 Apparent features of optical coherence tomography (OCT) and fluorescein angiography (FFA) for neovascular age-related macular degeneration (nAMD)

Features	OCT (index test)	FFA (reference standard)
Accuracy	High?	Reference standard
Invasiveness	Non-invasive	Invasive
Knowledge and skills needed to interpret	Moderate	High
Interpretable	Most tests	Nearly all tests
Cost	Low to moderate	Moderate
Side effects	None	Allergy (rarely anaphylactic shock)

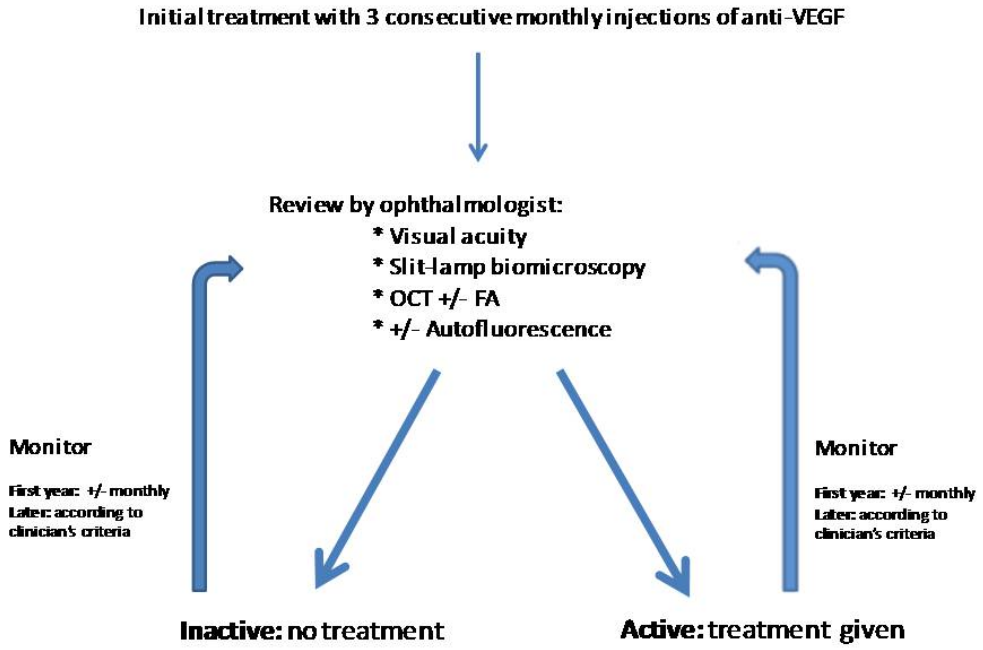
Treatment and monitoring of nAMD

When active nAMD is confirmed, treatment with anti-VEGF therapy is initiated.[8,9] For all patients with nAMD it is common practice to use three consecutive (monthly) intravitreal injections of anti-VEGF therapy, and then the patient is reassessed to evaluate whether or not the disease is active (i.e., neovascularisation leaking fluid/blood at the macula) or inactive (Figure 2). For this purpose, both FFA and OCT may be used, although the latter more often than the former, according to the guidelines of the Royal College of Ophthalmologists.[1] Studies that have a large influence in current practice used visual acuity and OCT at monthly intervals and FFA at quarterly intervals to decide on the need for re-treatment. In some units OCT is the only test performed to determine activity of the neovascular process in clinical practice; in some centres FFA is performed in selected cases during the monitoring phase. Other technologies such as fundus autofluorescence may also be used at baseline and at variable intervals during the follow-up of these patients as areas of atrophy in the RPE (difficult to detect clinically but easily observed on autofluorescence images) could be associated with fluid in the retina in the absence of active nAMD.

If fluid is not seen intraretinally or subretinally, further treatment is not given and the patient is followed thereafter regularly. The timing of follow-up visits is variable, typically every four weeks for the first year, extending the intervals after the second year. Varying intervals have been proposed, such as “treat and extend” strategy, where if there is no active disease no treatment is given and the monitoring intervals are progressively extended. If the disease is judged to be active, further injections of anti-VEGF are given. Either a single or three injections are administered if activity is detected on follow-up and then the patient returns to the monthly monitoring scheme. The possibility of using visual acuity (without imaging tests) as the only test to guide treatment during monitoring (i.e., treatment would be given if there is

a loss of >5 letters from best previously observed visual acuity) has been modelled using data from published trials for nAMD.[10] The authors concluded that an individualised visual acuity-guided regimen could sustain visual outcomes and improve cost-effectiveness compared with current regimes.

Figure 2 Current monitoring pathway of nAMD



3.2.2 Current service cost

Table 2 shows an estimation of unit costs associated with current diagnosis and monitoring care pathways. A first referral visit to a hospital eye service will involve an eye examination and is costed at £106. In addition, OCT and FFA tests can be indicated, with the overall cost for the first visits ascending to £274.71. A follow-up monitoring visit can involve a face-to-face attendance with an ophthalmologist and an OCT test only (£131). However, if an FFA is indicated, the monitoring visit will cost £248.27. Without doubt the major cost category is given by the treatment cost. There are two possible anti-VEGF treatments: ranibizumab and bevacizumab at £742.17 and £50 per injection, respectively. NICE guidelines advocate for the use of ranibizumab unless individual sight is heavily deteriorated. It should be noted that special cost arrangements are in place and a reduced cost for ranibizumab is agreed under a patient access scheme negotiated between the manufacturer and the Department of Health. Under this agreement the cost of ranibizumab to the UK NHS (confidential) is significantly lower than the

list price given above. The cost of bevacizumab is based on that of a compounded product as supplied by different compounding pharmacies in the UK.

Table 2 Diagnosis and monitoring costs associated with nAMD health care

	Unit costs (£ 2011-12)		
	Diagnosis	**Monitoring**	**Source**
Ophthalmologist visit	£106.18	£79.74	National Schedule of Reference Costs - Year 2011-12 - Ophthalmology - Consultant Led: First Attendance or follow-up Non-Admitted Face-to-face - NHS Reference Costs 2011-12. (HRG BZ23Z Minor Vitreous Retinal Procedures)
FFA	£117.26	£117.26	
OCT	£51.27	£51.27	NHS Reference Costs 2011-12. (HRG RA23Z Ultrasound Scan, less than 20 minutes)
Medication ranibizumab (Lucentis®)		£742.17	Ranibizumab (Lucentis®). Source: BNF (accessed 9/5/2013) Lucentis® (Novartis) Solution for intravitreal injection, ranibizumab 10 mg/mL, net price 0.23-mL vial = £742.17
Medication bevacizumab (Avastin®)		£50.00	As supplied by compounding pharmacies. Manufacturer's list price not applicable

3.2.3 Variation in service and/or uncertainty about best practice

Once nAMD has been diagnosed, monotherapy with an anti-VEGF drug (administered into the vitreous) is the current standard of care. Ranibizumab is highly effective and recommended by current guidelines. Bevacizumab remains unlicensed in the UK although its use worldwide reflects the fact that it is much cheaper than ranibizumab (as currently supplied for intravitreal administration) with similar efficacy.[8,9]

Retinal imaging with OCT before and after intravitreal administration of anti-VEGF therapy is regularly used.[11] Following anti-VEGF therapy a reduction of intraretinal and subretinal fluid is typically observed, often with rapid unification of the retinal layers and improvement /

restoration of the anatomical contours. This anatomical improvement is often accompanied by improvements in visual acuity.

The ultimate treatment goal when nAMD has already developed is to achieve restoration of central vision and prevent visual loss with normal or near normal foveal and macular anatomy. Complete cessation of exudation can result in good unification of the tissue layers, but most patients report difficulty with reading small print and other visually demanding tasks, even when tissue contours have been apparently restored. High resolution OCT scans obtained after anti-VEGF treatment show persistent abnormalities of the outer retina even though the tissues appear to be fluid free. In cases where localised atrophy and fibrosis have already occurred, considerable impairment of central visual function can remain despite the achievement of a fluid free macula.

Patients who have been treated with anti-VEGF therapy should be examined at regular intervals. Although most clinicians will use OCT for monitoring patients with nAMD, there is probably large variability on the tests used, e.g., biomicroscopy of the fundus, FFA, and fundus photography.

As explained above, patients treated with anti-VEGF injection should receive injections monthly for the first three months and, thereafter, should be monitored monthly. If active nAMD is present treatment should be continued, and if there is no active exudative AMD, observation at monthly intervals is recommended. The use of technologies, including OCT, FFA and fundus autofluorescence (FAF) during the follow-up of these patients is variable as it depends on clinical findings, the judgment of the treating ophthalmologist, and the clinical pathways established at different centres. The workload associated with such contemporary AMD services is significant and is expected to increase, as the best outcomes are achieved with monthly follow-up visits. It is expected that these follow-up visits may continue for as long as four years or longer. The pressure on resources and service delivery in the AMD clinics is expected to become even more intense as many patients cannot be discharged, and there is a need to accommodate new incident cases. The regular monthly follow-up for AMD patients under treatment, in order to maintain efficacy, is demanding. This situation is likely to be further aggravated by the impending treatments with intravitreal therapies of macular oedema secondary to diabetic retinopathy and retinal vein occlusion. As such the problem seems more acute than was originally envisaged, and is expected to get worse. It has been suggested engaging non-medical staff (optometrists, nurses, technicians) to undertake some of the duties in the AMD clinic in order to increase capacity. Such roles include clinical assessments, especially re-treatment decision making.

3.2.4 Relevant national guidelines, including National Service Frameworks

Subsequent to the technology appraisal and issuing of guidance by the National Institute for Health and Care Excellence (NICE), ranibizumab has been widely adopted as the treatment of choice for subfoveal nAMD in the UK.[7] However, the high cost of ranibizumab, along with the positive clinical experience with bevacizumab, has stimulated a debate on whether bevacizumab could be used in practice.

In the UK, guidelines for the management and treatment of nAMD were published by the RCO in 2009, and in 2013 were undergoing revision.[1] According to the RCO guidelines, FFA interpreted by an ophthalmologist is the method of choice and reference standard test to diagnose nAMD. Occasionally, indocyanine green angiography is associated with FFA as part of the reference standard when particular phenotypes of nAMD are suspected, including RAP and IPCV. In addition to FFA, current guidelines recommend using OCT at diagnosis. During follow-up and monitoring of disease activity after treatment the current guidelines recommend the use of OCT mainly, and FFA at the discretion of the clinician.

3.3 Description of technologies under assessment

3.3.1 Reference standard - fundus fluorescein angiography (FFA)

FFA is currently the reference standard for diagnosing CNV in AMD. A fluorescein angiogram is a sequence of images captured of the fundus over a ten minute period after injection of the non-toxic dye fluorescein isothiocyanate into a suitable peripheral vein.

Neovascular lesions are classified by their location with reference to the foveal avascular zone – extra-foveal, juxtafoveal or subfoveal. Lesions lying more than 200μm from fixation are defined as extrafoveal, and may also be described as juxtafoveal or subfoveal when immediately adjacent to or involving the geometric centre of the fovea, respectively. Neovascular lesions located away from the macula are termed peripheral and those around the optic nerve juxtapapillary. A more refined classification of the neovascular lesion is obtained by describing the composition of the exudative lesion after stereoscopic review of the entire sequence of the angiogram. The exudative lesion is defined as the area occupied by the neovascular complex, any associated blood, thick exudate and pigment epithelial detachments that are contiguous to the neovascular complex and obscure its margins. The neovascular complex can, therefore, consist of retinal angiomatous proliferation (RAP), choroidal neovascularisation (CNV) and idiopathic polypoidal choroidal vasculopathy (IPCV).

The classification of neovascular AMD lesions is based on the temporal and spatial features of the patterns of fluorescence as observed on the FFA. CNV lesions are classified according to their location relative to the fovea (see above), and pattern of fluorescein angiographic leakage. The majority of CNVs occur subfoveally.

Classic CNV is said to be present when an area of well delineated hyperfluorescence appears in the early phases of the FFA, usually before seconds have elapsed following injection of the fluorescent dye into a peripheral vein. Most commonly, classic CNV represents new vessels that have breached the RPE and lie in the subretinal space. Sometimes a typical lacy pattern of hyperfluorescence is observed in the very early phase of the angiogram which corresponds to the vascular profiles before the fluorescein has leaked out of these vessels and obscured the margins. Classic CNV also leak aggressively and hence there is considerable pooling of fluorescein dye in the subretinal space in late frames of the angiogram.

Occult CNV as its name suggests, refers to the presence of leakage without clear evidence of neovascular profiles in the early angiographic images. Two types of occult leakage are recognised. The first is a characteristic stippled hyperfluorescence which occurs early and is located at the level of the RPE. The RPE layer is elevated and in the later phases of the angiogram there is increasing hyperfluorescence and pooling of dye in the subretinal pigment epithelial space. The pattern of leakage suggests new vessels between Bruch's membrane and the RPE and it is therefore considered to be a fibrovascular pigment epithelial detachment (FPED). The second pattern of occult leakage is a more diffuse hyperfluorescence with poorly demarcated boundaries which occurs late in the angiographic phase, generally after two minutes have elapsed since injection of dye. There is no corresponding hyperfluorescence in the early frames and there is shallow elevation of the RPE. This type of leakage is referred to as late leakage of indeterminate origin (LLIO). Many lesions are mixed showing combinations of classic and occult features. It is now common practice to classify lesions by presence or absence of classic and or occult CNV. In the absence of any occult CNV, lesions are termed classic with no occult (100% classic) and conversely occult with no classic (0% classic).

When CNV is mixed the lesion is classified by the proportion of classic. When the lesion is composed primarily of classic CNV (i.e. classic greater than 50%) it is termed predominantly classic. When there is 1 to 49% classic the lesions are termed minimally classic.

Retinal angiomatous proliferation (RAP) One type of neovascularisation that has been well recognised by the use of high speed video angiography using the scanning laser ophthalmoscope is the RAP lesion. RAP is seen commonly as a round area of intraretinal

telangiectatic, dilated blood vessels located juxta- or extrafoveally. On viewing stereo pairs of images, the vessels are often seen to turn sharply from the inner retina towards the choroidal interface. Except in early stages, RAPs are associated with PEDs. They leak and hence the adjacent retina is usually disrupted with cystoid spaces. ICGA is a helpful test to determine the presence of RAP.

Idiopathic polypoidal choroidal vasculopathy (IPCV) Polyps are seen as focal, round areas of abnormal dilated choroidal vessels, often associated with large areas of lipid deposition and haemorrhage. The presence of haemorrhagic PED is highly suggestive of the presence of this phenotype. These are best visualised by ICGA.

3.3.2 Optical coherence tomography (OCT)

OCT was developed at the Michigan Institute of Technology, USA in 1991. It is a light-wave based technology producing cross-sectional images of the retina with scan rates and resolution parameters that have greatly improved over the last ten years. OCT is a non-invasive, non-contact visual test that requires around 5-10 minutes to assess both eyes.[12] From the investigator's point of view it is user friendly (e.g., OCT is easier to do than FFA), typically undertaken by trained medical photographers or ophthalmic imaging technicians, and interpreted by ophthalmologists. Automated analysis can also be used.

There are two main types of OCT system. The earlier time domain (TD) system, available from 1995, had an image rate of 100 to 400 scans per second and provided information for a limited view of the retina by taking six scans radially-oriented 30 degrees from each other with a resolution in the range of 10 to 20 µm.[12] The newer system, spectral domain (SD) OCT, has been available since 2006. Improvements with this system include (i) a faster scan speed of approximately 27,000 scans per second, (ii) the ability to scan larger areas of the retina by taking several horizontal line scans such that there are no 'missed areas', (iii) increased resolution at 5 µm, and (iv) 'real time registration', which was not previously available with TD-OCT.[12] The real-time registration feature enables the identification of specific anatomical locations on the retina, against which subsequent tests may be evaluated, which is of particular importance in the monitoring of patients.[12] Compared with TD-OCT, the faster scan speed of SD-OCT enables the collection of additional information on larger regions of the retina and eliminates image distortion arising from patient movement, while the improved resolution allows for a clearer and more distinguishable view of retinal layers, with the possibility of detecting earlier signs of disease.[12]

3.3.3 Identification of important sub-groups

There are different sub-groups of patients with nAMD. They are diagnosed according to FFA findings, and are described above. Subgroup classification depends on the location (extra-, juxta-, and subfoveal) and type of neovascularisation (classic and occult choroidal neovascularisation, retinal angiomatous proliferation (RAP), and idiopathic polypoidal choroidal vasculopathy (IPCV)), which could be mixed in different combinations. Although the initial treatment is similar for all sub-groups (with anti-VEGF therapy), the natural history and progression after treatment are different. It is also possible that the performance of diagnostic technologies may be different among sub-types of nAMD. OCT is not currently used in isolation to identify sub-groups.

3.3.4 Current usage in the NHS

Both FFA and OCT are currently used in the NHS to diagnose and monitor patients with nAMD. They are recommended technologies to provide standard care. FFA is essential for diagnosis of the condition. Regarding monitoring, FFA is less commonly used than OCT.

3.3.5 Anticipated costs associated with intervention

Table 3 presents an estimation of the number of visits in a lifetime of the population. Based on Census, nAMD prevalence and Interim Life Table data it is possible to estimate the number of visits for the population lifetime. Calculations in Table 3 are for England and Wales, based on 2011 data and assumed that every individual with nAMD would contact NHS services. This estimation resulted in 33.7 million visits. If OCT was conducted at every monitoring visit this would result in an undiscounted lifetime cost of above £1.7 billion (e.g. £51.27 (see Table 2) times 33.7 million).

Table 3 **nAMD prevalence and lifetime total number of monitoring visits for England and Wales**

	Population for England & Wales, 2011 Census-based estimates[13]	nAMD prevalence rates[6]	Number nAMD cases	Life expectancy[14]	Total number of monthly monitoring visits (lifetime)
Men					
Age					
65 to 69	1,096,335	0.38%	4,166	16.64	833,215
70 to 74	1,027,959	1.40%	14,391	13.06	2,259,454
75 to 79	810,590	2.63%	21,319	9.87	2,515,585
80to 84	557,203	5.56%	30,980	7.16	2,664,322
85 to 89	295,680	5.56%	16,440	5.07	1,002,828
90 to 99	333,448	5.56%	18,540	3.00	667,430
Total males					**9,942,833**
Women					
Age					
65 to 69	1,154,292	0.92%	10,619	19.15	2,442,482
70 to 74	1,140,959	1.42%	16,202	15.20	2,948,694
75 to 79	976,657	2.17%	21,193	11.59	2,945,891
80to 84	788,087	10.50%	82,749	8.46	8,440,412
85 to 89	532,677	10.50%	55,931	5.95	3,971,107
90 to 99	717,989	10.50%	75,389	3.36	3,015,554
Total females					**23,764,139**
Total overall population					**33,706,973**

3.4 Alternative tests

3.4.1 Clinical evaluation (with slit-lamp biomicroscopy with or without use of diagnostic contact lens and evaluation of patients' symptoms)

The onset of exudative AMD is heralded by the appearance of central visual blurring and distortion. Most patients will complain that straight lines appear crooked or wavy. Sometimes patients do not notice visual symptoms when the first eye is affected. When nAMD occurs in the second eye, patients suddenly become limited in their daily activities, e.g., reading, driving, and seeing fine detail such as facial expressions.

Examination of the macula usually reveals fluid and or lipid (yellow deposition) and/or blood. Other features of AMD such as drusen and pigmentary irregularities are most often present. Sometimes these latter features are not observed once exudative AMD has supervened or in certain phenotypes such as IPCV. However, the fellow eye would usually exhibit some or all of these AMD early clinical signs (drusen and RPE changes) and their presence is helpful in confirming that the neovascular lesion is due to AMD (again with the exception of IPCV where the fellow eye may also be normal). Following slit-lamp biomicroscopy the presence or absence of the following signs should be noted:

- Subretinal or sub-RPE neovascularisation which may be visible as a dark grey lesion. Occasionally the lesion will have a dark pigmented edge which is thought to be due to proliferation of the RPE at the edge of the membrane.
- Serous detachment of the neurosensory retina.
- RPE detachment.
- Haemorrhages - subretinal pigment epithelial, subretinal, intraretinal or preretinal. Breakthrough bleeding into the vitreous may also occur, indicating most often the presence of IPCV.
- Hard exudates (lipids) within the macular area related to any of the above, and not related to other retinal vascular disease.
- Epiretinal, intraretinal, subretinal or sub-pigment epithelial scar/glial tissue or fibrin-like deposits.
- Retinal angiomatous proliferations: red, round, extra- or juxtafoveal lesions located within the retina
- Polyps: red, round lesions located underneath the RPE or protruding through the RPE layer.

3.4.2 Visual acuity (for monitoring)

Visual acuity (VA) is a measure of the spatial resolution of the visual processing system. VA is tested by requiring the person whose vision is being tested to identify characters (like letters and numbers) on a chart from a set distance. Chart characters are typically represented as black symbols against a white background (for maximum contrast). The distance between the person's eyes and the testing chart is set at a sufficient distance to approximate infinity in the way the lens attempts to focus.

3.4.3 Amsler chart

The Amsler chart is a grid of horizontal and vertical lines used to monitor a person's central visual field. It is a diagnostic tool that aids in the detection of visual disturbances caused by changes in the retina, particularly the macula (e.g. macular degeneration). In the test, the person looks with each eye separately at the small dot in the center of the grid. Patients with macular disease may see wavy lines or some lines may be missing. Amsler grids are supplied by ophthalmologists, optometrists or from web sites, and may be used to test one's vision at home.

3.4.4 Colour fundus photographs

Colour fundus photography provides a record of the appearance of the macular retina. Stereoscopic images of the macula viewed appropriately can help localise pathology to the different tissue layers. For the purposes of recording macular pathology stereoscopic pairs of images taken at 35 degrees centred on the macula are recommended. Red-free images (RF) can help detect some features of the fundus associated with nAMD, such as haemorrhages.

3.4.5 Infra-red reflectance (IR)

Confocal near-infrared fundus reflectance (NIR) is a non-invasive *en face* imaging technique using an 830 nm diode laser capable of visualising subretinal pathology. In contrast to visible wavelength illumination, fundus reflectance may be up to ten times higher in the near infrared wave-length, and is then largely independent of melanin content, which advances the visibility of deep fundus structures.

3.4.6 Red-free images (RF) or blue reflectance

Mentioned in section above on colour fundus photographs.

3.4.7 Fundus autofluorescence imaging (FAF) or blue reflectance

This test can give an indication of the health of the RPE. The conventional fundus autofluorescence (FAF) signal (obtained with 488nm) originates, predominantly, from lipofuscin in RPE cells. The near-infrared autofluorescence (NIA) signal originates,

predominantly, from melanin in the RPE, with some contribution from choroidal melanin. Increased FAF represents accumulation of lipofuscin and suggests that the RPE cells are beginning to fail. Absence of FAF and NIA signal, which appears as black areas in FAF and NIA images, is due to loss of RPE cells. The finding of patches of absent autofluorescence may explain central scotoma patterns. While different patterns have been described in early and late AMD the exact diagnostic performance of autofluorescence is yet to be determined. The role of FAF may be more important in monitoring patients undergoing anti-VEGF therapy to evaluate atrophy, e.g., for potential discontinuation of treatment.

3.4.8 Indocyanine green angiography (ICGA), dynamic high speed or digital subtraction ICGA (DS-ICGA)

Indocyanine green (ICG) is an alternative dye to fluorescein which is used to visualise the choroidal circulation. This dye binds to plasma protein and hence does not egress easily through the fenestrae of the choroidal vessels, remaining within the vascular compartment. ICGA is obtained using longer wavelengths than FFA and, thus, can penetrate through areas of fluid/blood, permitting visualisation of pathology in circumstances where fluorescein may not. ICG also has some limitations and very thick blood or pigment can reduce or block transmission of the ICG infrared wavelength and the emitted light is of lower intensity compared with that of fluorescein. The use of the scanning laser ophthalmoscope (SLO) with video capture can however yield images of high resolution. Video ICGA also allows better imaging of RAP. As ICG dye does not leak into the subretinal and subpigment epithelial spaces to the same extent as fluorescein the enhanced definition of the vascularised tissue as a hotspot is possible and a combination of FFA and ICGA can produce complementary information. A dose of 25mg of ICG in aqueous solution is usually injected intravenously and images acquired for up to 30 minutes.

3.4.9 Preferential hyperacuity perimetry (PHP)

Preferential hyperacuity perimetry is a psychophysical test of macular function that exploits the ability of the human visual system to perceive even minute differences in the relative localisation of two objects in space; a phenomenon termed hyperacuity. When there is separation of the retinal layers through breakdown of the blood retinal or blood retinal pigment epithelial barriers, distorted vision is the consequence. Through presentation of lines with artificial distortions of different intensities on the PHP, the presence of a real distortion in the patient's central visual field can be detected as the brain ignores the smaller deviation when a larger one is introduced.

In a PHP test, the macula is scanned with a succession of stimuli, each stimulus consisting of a series of dots arranged along a vertical or horizontal axis. In each stimulus, a small number of dots are misaligned, thereby creating an artificial distortion (bump or wave). The examinee's task is to perceive these artificial distortions and mark their locations on the visual field. When a stimulus is projected on a healthy portion of the retina, the examinee identifies the artificial distortion and is likely to mark a correct location. If the stimulus is projected on a damaged region of the retina, a pathological distortion may be perceived instead of the artificial distortion, especially if the pathological distortion is more prominent than the artificial distortion. The examinee may then mark a location that is distant from the artificial distortion, indicating that a pathological distortion may have been perceived. By manipulating the amplitude of artificial distortions, the amplitude of the pathology in the area of interest can be quantified. At the end of the test, comparison of the set of erroneous responses against a normative data base is used to determine if test results are within normal limits.

3.4.10 Microperimetry

One conventional measure of vision is subjective visibility thresholds of small, short-duration stimuli as performed by conventional automated static perimetry. In conventional perimetry, retinal localisation of a stimulus is implied indirectly from the assumed retinal location of fixation. This approach can work well when fixation is stable and foveal. However, loss of fixation stability or foveal vision, such as occurs commonly in nAMD, complicates the measurement of macular function with conventional perimetry. Accurate correspondence between retinal structures and visual function requires simultaneous imaging of the fundus. Microperimetry includes real-time automated tracking of the fundus and appropriate compensation of the location of stimulus presentation at predefined retinal loci.

3.5 Care pathway

See above Section 3.2.1, Management of disease: Diagnosis of nAMD. Currently, patients with suspected nAMD seen by optometrists or other health professionals will be referred to secondary care where ophthalmologists with expertise on AMD will perform the following tests: visual acuity measurement, slit-lamp biomicroscopy and, if the diagnosis of nAMD remains a possibility, FFA and OCT. The FFA and OCT imaging tests are used to confirm the diagnosis, and they also provide a baseline reference for future comparisons during the follow-up of the patient. Alternative technologies are used at presentation in some units, e.g., fundus autofluorescence imaging, to evaluate the status of the retinal pigment epithelium (RPE) which may have prognostic implications.

4 DEFINITION OF THE DECISION PROBLEM

4.1 Decision problem

New treatments for neovascular age-related macular degeneration (nAMD) have been approved by NICE for use in the NHS. These treatments often require repeated injections of anti-vascular endothelial growth factor (anti-VEGF) over a period of years, with frequent monitoring greatly increasing the demand on secondary care AMD services.

Fundus fluorescein angiography (FFA), an invasive test, is the reference standard recommended for detecting nAMD at initial presentation and also for detecting recurrent activity at some monitoring visits (e.g. quarterly, or according to clinician criteria). Optical coherence tomography (OCT) is a non-invasive test now widely used for detecting nAMD both at initial presentation and for detecting recurrent activity during monitoring visits. Two OCT systems are in use. The more recently introduced spectral domain OCT (SD-OCT) incorporates a number of improvements over the earlier time domain OCT (TD-OCT). Depending on the performance of OCT, in some situations its use could possibly replace that of FFA. Also, as the interpretation of OCT images is more straightforward than that of FFA, it could potentially be interpreted by other health professionals (e.g. medical photographers, nurses).

However, the value of OCT has not been well-defined and given the burden of monthly lifelong monitoring by ophthalmologists, involving multiple tests, an assessment of the role of OCT in the diagnosis, monitoring and guiding of treatment for nAMD is needed.

4.1.1 Index test(s)

The index test considered was OCT, either alone or in combination with alternative tests as described below. Both time-domain OCT (TD-OCT) and spectral-domain OCT (SD-OCT) were considered.

4.1.2 Population

The population considered was people with newly suspected nAMD or those previously diagnosed with the disease and under surveillance monitoring.

The setting considered was secondary care.

4.1.3 Relevant comparators

The alternative tests considered included the following examinations:

- Clinical evaluation (with slit-lamp biomicroscopy (SLB) with or without use of diagnostic contact lens and evaluation of patients' symptoms);
- Visual acuity (VA) (for monitoring);
- Amsler chart;
- Colour fundus photographs;
- Infra-red reflectance (IR);
- Red-free images (RF) or blue reflectance;
- Fundus autofluorescence imaging (FAF);
- Indocyanine green angiography (ICGA), dynamic high-speed or digital subtraction ICGA Angiography (DS-ICGA);
- Preferential Hyperacuity Perimetry (PHP); and
- Microperimetry.

4.1.4 Reference standard

The reference standard considered was ophthalmologist interpreted FFA. FFA is generally acknowledged as being the recognised reference standard for detecting nAMD. The Royal College of Ophthalmologists states in its guidelines for management of AMD that FFA is currently the reference standard for diagnosing exudative disease.[1] However as few studies reported individual ophthalmologist-interpreted FFA (rather than reading centre interpreted FFA), studies using FFA as the reference standard but with unclear information about which type of healthcare professionals interpreted the images were also considered.

4.1.5 Outcomes

The following outcomes were considered for the use of OCT at presentation and during follow-up of patients with nAMD:

- Diagnostic accuracy (e.g. sensitivity, specificity, likelihood ratios, diagnostic odds ratio);
- Clinical effectiveness (e.g. visual acuity, anatomical control of the disease, patient reported outcomes);
- Interpretability of the test – to be defined as in included studies, considering the ability to acquire a quality image that can be interpreted or analysed;
- Acceptability of the test – to be defined as in included studies, considering users and healthcare providers' perspective;
- Proportion of participants not able to receive the diagnostic test (due to an eye condition e.g. lens or other media opacity, or personal circumstances e.g. wheelchair bound).

The evidence for the use of OCT was considered separately for the purposes of diagnosis and monitoring.

4.1.6 Key issues

The key issues to be addressed are:

- How good a test is OCT, when used either alone or in combination with alternative tests, in the diagnosis of people newly presenting with a suspicion of nAMD?
- How good a test is OCT, when used either alone or in combination with alternative tests, in detecting recurrent nAMD activity during surveillance monitoring of people previously diagnosed with the disease?
- Is SD-OCT a better test than TD-OCT?
- Could OCT images be interpreted by other health professionals in addition to ophthalmologists?
- Could OCT replace FFA in some situations in the diagnostic and/or monitoring pathways?
- How cost-effective are strategies involving OCT, both in the diagnostic and monitoring pathways?

4.2 Overall aims and objectives of assessment

The overall aim of the review was to determine the optimal role of OCT in (i) the diagnosis of people newly presenting with suspected nAMD and (ii) in monitoring those previously diagnosed with the disease.

Specific research objectives were:

- To determine the diagnostic performance of OCT, alone or in combination with alternative tests, in detecting nAMD, including accuracy, interpretability, and acceptability;
- To determine the performance of OCT and/or other alternative tests in the monitoring of the disease post-diagnosis, specifically in detecting activity of the disease and the need for further treatment;
- To determine the performance of other health professionals (e.g. medical photographers, nurses) compared with ophthalmologists in interpreting OCT findings;
- To model the effects of using OCT and/or other alternative tests in the diagnosis and management of the disease and estimate the relative cost-effectiveness of alternative diagnostic and monitoring strategies, including determination of an optimal cut-off point for sensitivity and specificity for use in practice, and the alternative timing between tests during monitoring; and
- To identify future research needs.

5 METHODS FOR REVIEWING TEST PERFORMANCE

Methods were in accordance with the protocol, which is presented in Appendix 1.

5.1 Identification of studies

Published, unpublished and ongoing studies were identified from literature searches of electronic databases (from 1995 onwards) and appropriate websites. The search strategies were designed to be highly sensitive, including appropriate subject headings and text word terms that reflected both the clinical condition and diagnostic tests under review. There were no language restrictions. Databases searched included MEDLINE, MEDLINE In-Process, EMBASE, Biosis and Science Citation Index (SCI) for all reviews. The Cochrane Central Register of Controlled Trials (CENTRAL) was searched for additional reports of RCTs for the effectiveness review and PsycINFO and ASSIA for patient acceptability data. The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), MEDION and HTA database were searched for relevant systematic reviews and HTA reports. Abstracts and presentations from recent conferences (2009 onwards) of the American Academy of Ophthalmology (AAO), the Association for Research in Vision and Ophthalmology (ARVO), and the European Association for Vision and Eye Research (EVER) were also searched. The WHO International Clinical Trials Registry Platform (ICTRP), Clinical Trials.gov and EU Clinical Trials Register were searched for ongoing studies. Websites of professional organisations and manufacturers of optical coherence tomography (OCT) equipment were also consulted. Reference lists of all included studies were scanned and experts contacted for details of additional potentially relevant reports. The date of the final searches was March 2013. Full details of the search strategies used are provided in Appendix 2.

5.2 Inclusion and exclusion criteria

5.2.1 Types of studies

The following types of studies were considered:

(i) Diagnostic studies:

- Direct (head-to head) comparisons in which the index test and comparator test(s) are evaluated in the same study population. These could be fully paired (all study participants receive the index test, comparator test(s) and the reference standard) or not fully paired (participants receive only a subset of the tests, e.g. a randomised direct comparison in which study participants are randomly allocated to receive the index test or the comparator and all receive the reference standard.
- Indirect comparisons in which estimates of the accuracy of the respective tests are obtained in different study groups, e.g. two-gate or ‘case-control’ type studies where

different sets of criteria are used for those with and without the target condition. Indirect comparisons were to be considered if there was insufficient evidence from direct comparisons.

(ii) Studies reporting clinical effectiveness:

- RCTs evaluating outcomes when treatment was based on OCT compared with fundus fluorescein angiography (FFA) findings.

(iii) Qualitative studies evaluating patients' and/or clinicians'/healthcare professionals' acceptability and/or interpretability of the OCT tests.

5.2.2 Types of participants

The types of participants considered were people with newly suspected nAMD or those previously diagnosed with the disease and under surveillance monitoring.

The setting considered was secondary care.

5.2.3 Index tests

The index test considered was OCT, either alone or in combination with alternative tests as described below. Both time-domain optical coherence tomography (TD-OCT) and spectral-domain optical coherence tomography (SD-OCT) were considered.

5.2.4 Comparator tests

The alternative tests considered included the following examinations:

- Clinical evaluation (with slit-lamp biomicroscopy (SLB) with or without use of diagnostic contact lens and evaluation of patients' symptoms);
- Visual acuity (VA) (for monitoring);
- Amsler chart;
- Colour fundus photographs;
- Infra-red reflectance (IR);
- Red-free images (RF) or blue reflectance;
- Fundus autofluorescence imaging (FAF);
- Indocyanine green angiography (ICGA), dynamic high-speed or digital subtraction ICGA Angiography (DS-ICGA);
- Preferential Hyperacuity Perimetry (PHP); and
- Microperimetry.

5.2.5 Reference standard

The reference standard considered was ophthalmologist interpreted FFA. FFA is generally acknowledged as being the recognised reference standard for detecting nAMD. The Royal College of Ophthalmologists states in its guidelines for management of AMD that FFA is currently the reference standard for diagnosing exudative (neovascular) AMD.[1,15] However as few studies reported individual ophthalmologist-interpreted FFA (rather than reading centre interpreted FFA), studies using FFA as the reference standard but with unclear information about which type of healthcare professionals interpreted the images were also considered.

5.2.6 Types of outcomes

The following outcomes were considered for the use of OCT at presentation and during follow-up of patients with nAMD:

- Diagnostic accuracy (e.g. sensitivity, specificity, likelihood ratios, diagnostic odds ratio);
- Clinical effectiveness (e.g. visual acuity, anatomical control of the disease, patient reported outcomes);
- Interpretability of the test – defined as in the included studies, considering the ability to acquire a quality image that can be interpreted or analysed;
- Acceptability of the test – defined as in the included studies, considering users and healthcare providers' perspective;
- Proportion of participants not able to receive the diagnostic test (due to an eye condition e.g. lens or other media opacity, or personal circumstances e.g. wheelchair bound).

The evidence for the use of OCT was considered separately for the purposes of diagnosis and monitoring.

5.3 Data extraction strategy

Two reviewers (MC plus GM or AAB) screened the titles (and abstracts if available) of all reports identified by the search strategy. Full-text copies of all studies deemed to be potentially relevant were obtained and two reviewers (MC plus AAB or GM) independently assessed them for inclusion. Disagreements were resolved by consensus or arbitration by a third reviewer.

A data extraction form was developed and piloted. One reviewer (MC) extracted details of study design, participants, index, comparator and reference standard tests and outcome data, and a second reviewer (AAB or GM) checked the data extraction. Disagreements were resolved by consensus or arbitration by a third reviewer.

5.4 Critical appraisal strategy

Two reviewers (MC plus AAB or GM) independently assessed the risk of bias and applicability concerns of all included full-text diagnostic and monitoring studies using the updated quality assessment of diagnostic accuracy studies (QUADAS-2) checklist.[16] Any disagreements were resolved by consensus or arbitration by a third party. The original QUADAS checklist was developed for use in systematic reviews of diagnostic studies through a formal consensus method and was based on empirical evidence. Following anecdotal reports and feedback which suggested problems with QUADAS, the QUADAS-2 tool was developed. QUADAS-2 consists of four key domains covering (1) patient selection, (2) index test, (3) reference standard, and (4) flow of patients through the study and timing of the index test(s) and reference standard. Each domain is assessed in terms of the risk of bias. The first three domains are also assessed for concerns regarding their applicability in terms of whether (i) the participants and setting, (ii) index test, its conduct or interpretation and (iii) target condition as defined by the reference standard match the question being addressed by the review. Within each domain signalling questions are included to assist in making a judgment about the risk of bias, with the standard tool containing 11 such questions across the four domains.

Both the original and updated checklists were designed to be adapted to be more applicable to a specific review topic. For this review, QUADAS-2 was modified by adding an additional signalling question to domain 1 (patient selection) to assess whether participant pre-selection had been avoided. Domains 2 (index test), 3 (reference standard) and 4 (flow and timing) were retained in their entirety. Therefore the modified tool contained 12 signalling questions, with each worded so that a rating of 'Yes' was always optimal in terms of methodological quality. If any signalling questions within a domain were rated 'No' then that domain was judged to be at high risk of bias. With regard to question 9 in the modified tool (appropriateness of the time interval between the index test and the reference standard), it was agreed that to be considered appropriate, the time interval between the index test and reference standard should be no longer than one week. An example of the QUADAS-2 checklist used in this review is shown at the end of the protocol (Appendix 1).

We planned to assess the methodological quality of any RCTs reporting effectiveness outcomes that met our inclusion criteria using the Cochrane risk of bias tool.[17] This tool addresses six specific domains relating to methodological quality (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'). However no RCTs reporting effectiveness outcomes were identified that met our inclusion criteria.

5.5 Methods of data synthesis

The results of the individual diagnostic studies were tabulated and, where data allowed, sensitivity, specificity, predictive values, likelihood ratios and diagnostic odds ratios were calculated.

Summary receiver operating characteristic (SROC) curves were produced for each test where two or more diagnostic studies reported sufficient data. In the event of studies reporting 2x2 data (true positives, false positives, false negatives, true negatives) for a number of different cut off values we planned to select the most frequently used cut off value across studies. However this situation did not arise. Meta-analysis models were fitted using the hierarchical summary receiver operating characteristic (HSROC) model[18] in SAS version 9.1. A symmetric SROC model was used, which takes proper account of the diseased and non-diseased sample sizes in each study, and allows estimation of random effects for the threshold and accuracy effects. The SROC curves from the HSROC models were produced on the corresponding SROC plots. Summary sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios (DORs) for each model were reported as point estimate and 95% confidence interval (CI).

If numerical difficulties were encountered with the HSROC model and there was no evidence of a threshold effect then we planned to pool sensitivity and specificity using the weighted average method[19] Pooled likelihood ratios and DOR were to be calculated using the DerSimonian and Laird random effects method.[20] These analyses were to be carried out using Metadisc software,[21] with heterogeneity assessed using the I^2 statistic, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error.[22]

For relevant clinical outcomes reported based on use of the tests, where appropriate, we planned to use meta-analysis to estimate a summary measure of effect. Dichotomous outcome data were to be combined using the Mantel-Haenszel relative risk (RR) method and continuous outcomes were to be combined using the inverse-variance weighted mean difference (WMD) method. For the estimates of RR and WMD 95% confidence intervals (CIs) and p-values were to be calculated. Chi-squared tests and I-squared statistics were to be used to explore statistical heterogeneity across studies, with possible reasons for heterogeneity being investigated using sensitivity analysis. Heterogeneity is to be expected in diagnostic test accuracy studies, and random effects models were to be used to describe the variability across studies. However no studies reporting clinical outcomes based on use of the tests were identified that met our inclusion criteria.

Where a quantitative synthesis was considered inappropriate (e.g. studies reporting acceptability of tests), or not feasible, a narrative synthesis of results was provided.

6 ASSESSMENT OF DIAGNOSTIC AND MONITORING STUDIES

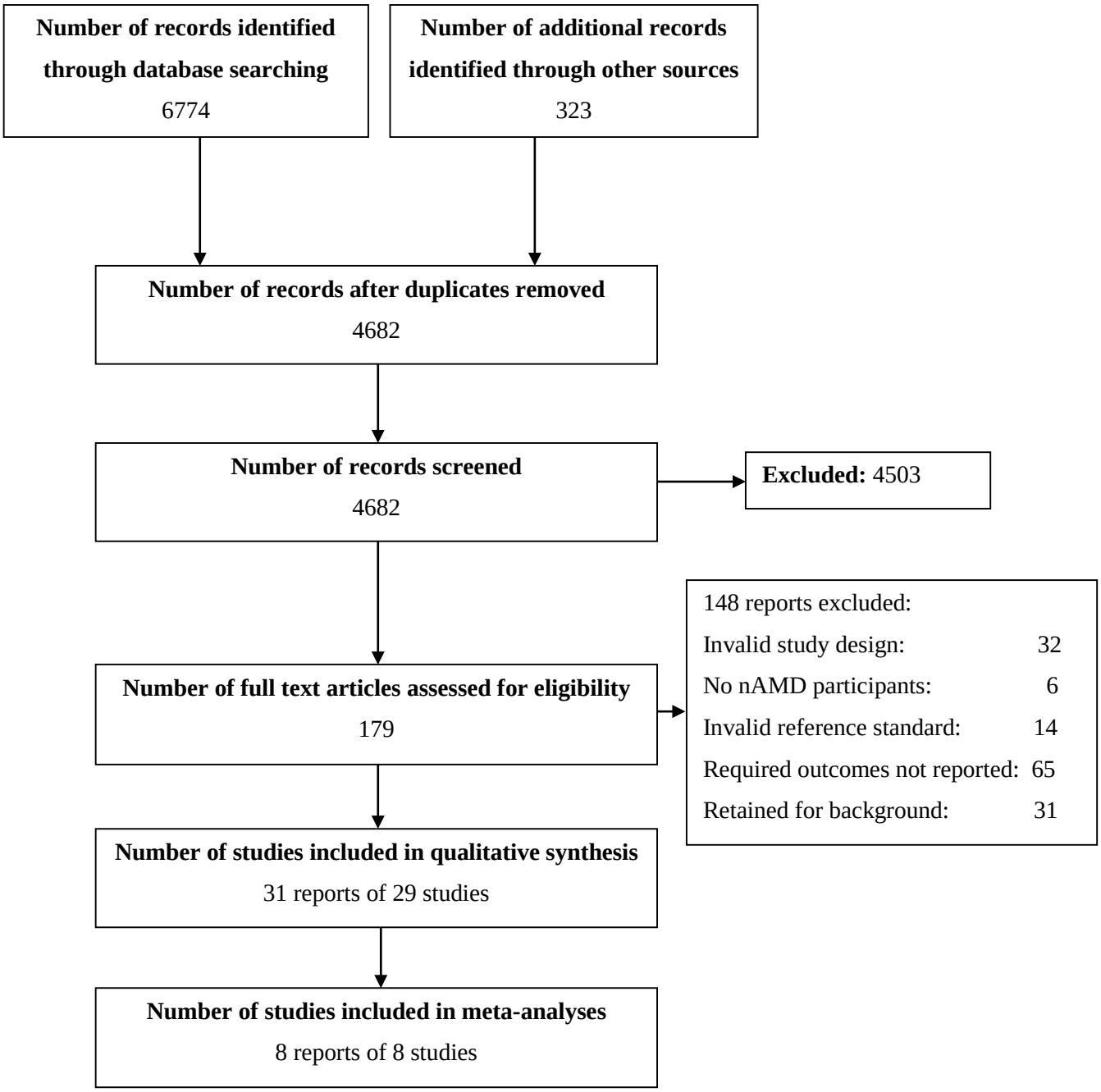
This chapter is structured as follows. Section 6.1 describes the quantity of research available for both diagnostic and monitoring studies together, sections 6.2 and 6.3 report the results for the diagnostic and monitoring studies respectively, while section 6.4 provides a summary of the chapter. Within each of the sections on diagnostic and monitoring studies there are subsections on the characteristics of the included studies, their risk of bias, diagnostic accuracy results (single tests; studies directly comparing tests; studies reporting combinations of tests) and other outcomes of interest.

6.1 Quantity of research available

6.1.1 Number and type of studies included

Appendix 3 lists the 29 studies, published in 31 reports, that met the inclusion criteria for the review of diagnostic and monitoring studies.[15,23-52] There were two reports of the studies by Cachulo et al.[24,46] and Torron et al.[49,50] Figure 3 shows a flow diagram outlining the screening process, with reasons for exclusion of full-text papers.

Figure 3 Flow diagram outlining the screening process



Twenty-seven studies (29 reports in total as two studies each had two associated reports) were full-text papers and two studies were only available as abstracts.[33,41] Four studies (five reports) were non-English language, with one each in Japanese,[28] Chinese,[25] German[36] and Spanish.[49,50] Of the 29 included studies, 22 (24 reports)[23-26,28,30,32-41,43-50] were diagnostic studies involving people with suspected nAMD and eight[15,27,29,31,42,44,51,52] were monitoring studies involving people previously diagnosed with nAMD and under follow-up surveillance. One study, by Salinas-Alaman et al.,[44] reported results for both diagnosis and monitoring.

6.1.2 Number and type of studies excluded

A list of full-text papers that were excluded along with the reasons for their exclusion is given in Appendix 4. These reports were excluded because they failed to meet one or more of the inclusion criteria in terms of the type of study, participants, test, reference standard or outcomes reported.

6.2 Assessment of diagnostic studies

6.2.1 Characteristics of the included diagnostic studies

Appendix 5 (Table a) provides details of the individual study characteristics for the 22 diagnostic studies. Table 4 provides summary information for these studies. Of the 22 studies, nine were prospective[23,24,26,32,38-40,44,45] and seven were retrospective.[33-35,37,38,48,50] Seven studies did not provide this information.[25,28,30,36,41,43,47] (The study by Loewenstein and colleagues[38] reported both a prospective and retrospective component.) In ten studies participant recruitment was consecutive.[32,33,37,38,41,43-45,47,48] The studies enrolled more than 2,000 participants. Twenty-one studies reported eye as the unit of analysis (1754 eyes), while one[41] reported patient as the unit of analysis (155 patients).

Table 4 Summary of the characteristics of the included diagnostic studies

Characteristic	Number	Number of studies
Participants enrolled	2124	22
Analysed (eyes)	1754	21
Analysed (patients)	155	1
Age: Median (range) of means/medians	76 (51.4 to 84.6)	15
Gender: male: female n (%)	742 (45.4%): 891 (54.6%)	14
Median (range) prevalence of nAMD	80.0% (17.2% to 100%)	13
Tests reported (number enrolled)		
OCT	1335	13
TD-OCT	1316	12
SD-OCT	19	1
ICGA	458	8
PHP	491	3
Colour fundus photography	185	1
Amsler Grid	98	1
FAF	62	1

Notes:

1. FAF, fundus autofluorescence; ICGA, indocyanine green angiography; OCT, optical coherence tomography; PHP, preferential hyperacuity perimetry; TD-OCT, time domain optical coherence tomography; SD, spectral domain optical coherence tomography.
2. The study by Kozak et al.[35] enrolled 654 participants (1,272 eyes analysed) with a diagnosis of suspected or confirmed macular oedema of various aetiologies but did not specify how many were nAMD. Of these, 541 eyes with a diagnosis of suspected or confirmed nAMD were included in the analysis and this number has been included in the above table as an approximation of the number of nAMD participants enrolled by this study.
3. The median (range) prevalence of nAMD was derived from 13 studies where this information was available at participant level. Studies reporting eye as the unit of analysis where it was not possible to ascertain the number of participants with nAMD or studies reporting results only at phenotype level were not included in these calculations.

Seven studies were undertaken in the USA,[26,33,35,37,39,40,43] three in the UK,[32,45,48] two each in Japan,[28,30] Austria[36,47] and Spain[44,50] and one each in Portugal,[24] Italy (involving eight centres),[41] South Korea[34] and China.[25] The remaining two studies were international, taking place in (a) seven centres in the USA, Germany, Israel, Austria and Portugal[23] and (b) 15 centres in Israel and the USA.[38] Of the three UK-based studies, two took place at the Royal Victoria Infirmary, Newcastle upon Tyne[45,48] while the third took place at King's College Hospital, London.[32] One of the UK-based studies, by Talks et al., involved a nurse-led, fast track screening clinic.[48]

The largest study was by Kozak et al.,[35] which reported time-domain optical coherence tomography (TD-OCT), was set in the USA and analysed 541 eyes, while the smallest was by Sulzbacher et al.,[47] reporting indocyanine green angiography (ICGA) and including only 13 eyes.

Across 15 studies reporting the mean or median age of the participants,[23-26,28,30,34-36,38,39,44,45,48,50] the median (range) of these values was 76 years (51.4 to 84.6 years). Fourteen studies involving 1633 participants provided information on gender, in which 742 (45.4%) participants were men and 891 (54.6%) were women.[23,24,26,28,30,34,35,38-40,44,45,48,50] The median (range) prevalence of nAMD across 13 studies where this information was available at participant level was 80.0% (17.2% to 100%).[23,24,26,32,34,37-40,43,44,48,50]

In three studies, by Cachulo et al.,[24] Do et al.,[26] and Padnick-Silver et al.[39] the inclusion criteria specified that participants were required to have previously diagnosed nAMD in the non-study eye.

Thirteen studies reported OCT (twelve TD-OCT;[24,26,32-37,39,44,45,48] one SD-OCT).[40] The study by Kozak et al., reporting TD-OCT, included a subset of patients who underwent additional examination with SD-OCT.[35]

Of the other tests reported, three studies reported preferential hyperacuity perimetry (PHP),[23,26,38] one reported colour fundus photography,[23] one Amsler grid,[26] one fundus autofluorescence imaging (FAF)[24] and eight ICGA.[24,25,28,30,41,43,47,50] Of the studies reporting more than one test, Cachulo et al.[24] reported TD-OCT, ICGA and FAF, Do et al.[26] TD-OCT, Amsler Grid and PHP, and Alster et al.[23] reported PHP and colour fundus photography. Two studies reported combinations of tests; Alster et al.[23] reported colour fundus photography plus visual acuity, while Sandhu et al.[45] reported TD-OCT plus colour fundus photography.

The 13 studies reporting OCT analysed 1262 eyes; in eight studies one eye per patient was analysed (n = 479 eyes) (all TD-OCT).[24,26,32-34,37,39,48] Eight studies reported detection of nAMD phenotypes (predominantly classic, minimally classic, occult CNV).[24,32,33,36,37,40,45,48] Four of these studies also reported detection of RAP.[24,33,36,37]

Of the eight studies reporting ICGA, seven used the eye as the unit of analysis (number of eyes analysed = 291).[24,25,28,30,43,47,50] In three of these studies one eye per patient was analysed (n = 109 eyes).[24,30,43] Three studies only reported detection of nAMD phenotypes: idiopathic polypoidal choroidal vasculopathy (IPCV);[30] occult CNV;[25] and type 2 CNV without an occult component.[47] The study by Parravano et al.,[41] with patient as the unit of analysis (n=155 patients), also only reported detection of an nAMD phenotype – retinal angiomatous proliferation (RAP).

The three studies reporting PHP analysed one eye per patient (n = 302 eyes),[23,26,38] as did the studies reporting colour fundus photography (n = 120 eyes),[23] Amsler grid (n = 46 eyes)[26] and FAF (n = 50 eyes).[24]

6.2.2 Risk of bias of the included diagnostic studies

All 20 full-text papers were assessed using a modified version of the QUADAS-2 tool containing 12 items. QUADAS-2 consists of four key domains covering (1) patient selection, (2) index test, (3) reference standard, and (4) flow of patients through the study and timing of the index test(s) and reference standard. Each domain is assessed in terms of the risk of bias and the first three domains are also assessed for concerns regarding their applicability in terms of whether they match the question being addressed by the review. Figure 4 presents a summary of the results for the QUADAS-2 risk of bias and applicability domains across the full-text diagnostic papers. Appendix 6 (Table a) presents the results of the risk of bias and applicability concerns for the individual studies.

No study was judged to have a low risk of bias across all domains; in three studies the risk of bias was judged to be unclear across all domains.[28,34,47] The domains in which the greatest number of studies were judged to be at high risk of bias were the patient selection domain (n = 11, 55%) and flow and timing domain (n = 8, 40%).

In the patient selection domain only one study[35] was judged to be at low risk of bias, while the majority were considered to have either a high (n = 11, 55%)[23,26,30,36-40,43,44,48] or unclear (n = 8, 40%)[24,25,28,32,34,45,47,50] risk of bias. Reasons for studies being judged to be at high risk of bias

included not enrolling a consecutive sample of participants,[26,36] not avoiding inappropriate exclusions[23,30,37-40,43] and not avoiding pre-selection of participants.[23,26,30,38,39,43,44,48]

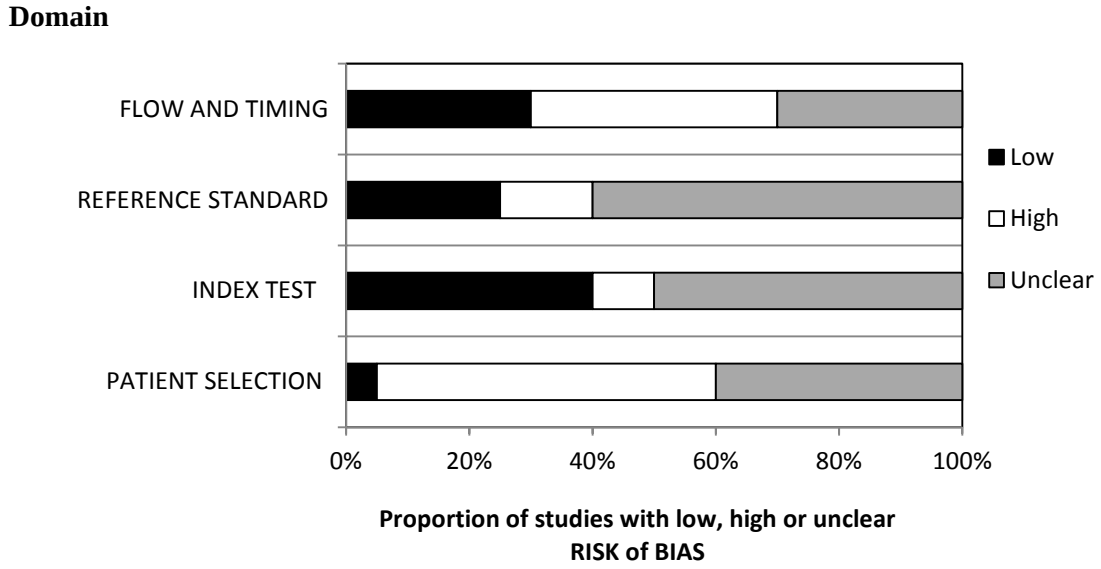
In the index/comparator test domain eight studies (40%) were judged to be at low risk of bias,[23,26,32,36,37,40,45,48] two (10%) were considered high risk of bias[43,50] while in half (n = 10, 50%) the risk of bias was considered to be unclear.[24,25,28,30,34,35,38,39,44,47] The reasons for the two studies being judged to be at high risk of bias was that the test (ICGA in both cases) was interpreted with knowledge of the results of the reference standard.

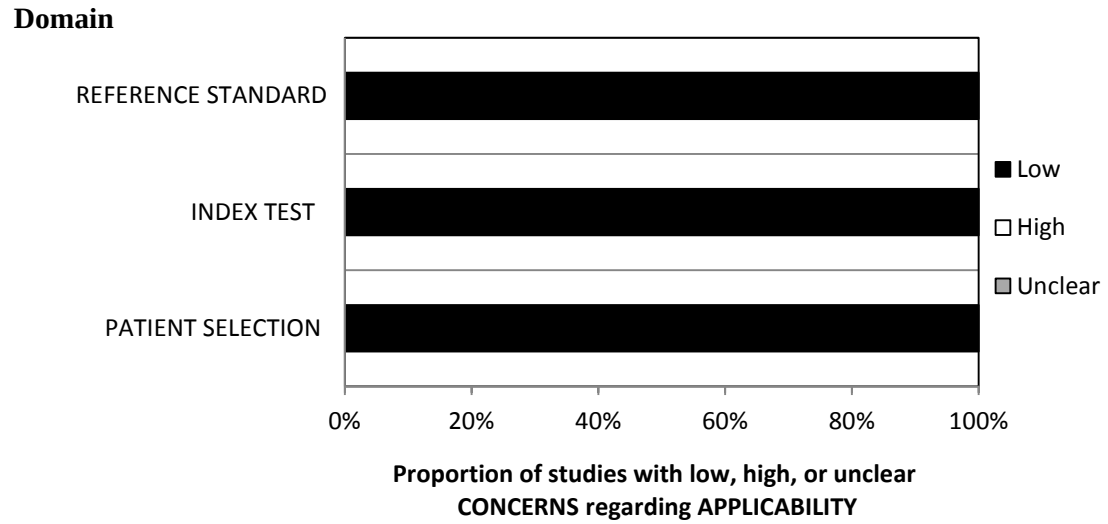
In the reference standard domain five studies (25%) were judged to be at low risk of bias,[23,26,32,36,45] three (15%) were considered high risk of bias[43,48,50] while in the majority (n = 12, 60%) the risk of bias was considered to be unclear.[24,25,28,30,34,35,37-40,44,47] The reasons for the three studies being judged to be at high risk of bias was that the reference standard test was interpreted with knowledge of the results of the index test (TD-OCT)[48] or comparator test (ICGA).[43,50]

In the flow and timing domain six studies (30%) were judged to be at low risk of bias,[25,30,36,37,40,43] while the majority were considered to have either a high (n = 8, 40%)[23,24,26,35,38,39,45,48] or unclear (n = 6, 30%)[28,32,34,44,47,50] risk of bias. Reasons for studies being judged to be at high risk of bias included an interval of more than one week between the index/comparator test and reference standard,[23,38] not all patients receiving the reference standard test[38] or not all patients being included in the analysis.[23,24,26,35,38,39,45,48]

All 20 diagnostic studies were judged to have low concerns for applicability regarding the patient selection, index/comparator test, and reference standard domains, in that the participants and setting, index/comparator test and target condition as defined by the reference standard were considered to match the question being addressed by the review.

Figure 4 Summary of risk of bias and applicability domains (diagnostic studies)





6.2.3 Results – diagnostic accuracy

Individual study results are presented in Appendix 7 (Table a).

Single tests

- **OCT**

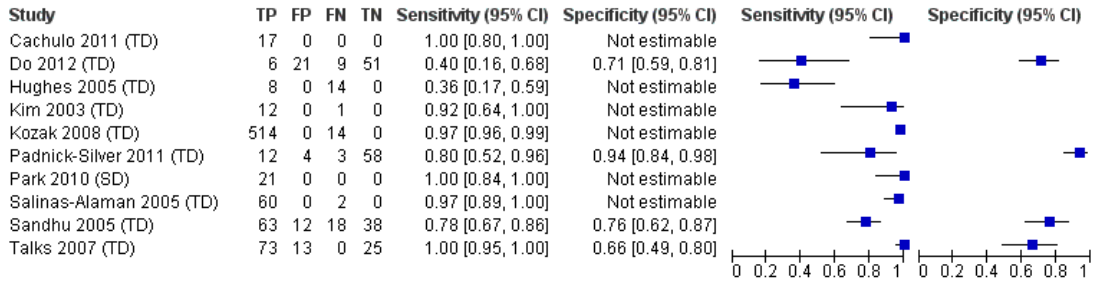
Thirteen studies, analysing 1262 eyes, reported the diagnostic accuracy of OCT in detecting nAMD (twelve TD-OCT;[24,26,32-37,39,44,45,48] one SD-OCT).[40] In eight studies one eye per patient

was analysed (n = 479 eyes) (all TD-OCT).[24,26,32-34,37,39,48] Eight studies reported detection of nAMD phenotypes.[24,32,33,36,37,40,45,48]

The median (range) prevalence of nAMD across nine OCT studies where this information was available at participant level was 100% (17.2% to 100%).[24,26,32,34,37,39,40,44,48]

Figure 5 shows a forest plot of the sensitivity and specificity of the individual studies (excluding three where information was only available at phenotype level).[33,36,37] Across these ten studies, the median (range) sensitivity and specificity values reported were 94.5% (36% to 100%) and 73.5% (66% to 94%) respectively. Only four studies (all TD-OCT) reported specificity. For TD-OCT, across the studies, the median (range) sensitivity and specificity values reported was 92.3% (36% to 100%) and 73.4% (66% to 94%), while the only SD-OCT study reported sensitivity of 100% and did not report specificity.

Figure 5 Individual study results for all OCT diagnostic studies reporting sensitivity and/or specificity



The studies shown in Figure 5 demonstrate heterogeneity across the sensitivities reported. The lowest sensitivity reported was by Hughes et al. (36%) and Do et al. (40%).[26,32] In the study by Hughes et al.,[32] set in the UK, 22 individuals were classed as nAMD by fluorescein angiography (FFA), seven with classic and 15 with occult CNV. TD-OCT detected six of the seven classic CNVs but only two of the 15 occult CNVs, hence the low overall sensitivity. The overall prevalence of nAMD in this study was 100%. Do et al.,[26] using TD-OCT in a study set in the USA, reported two separate sets of results, one for when the reference standard was fluorescein angiogram graded as positive by the reading centre irrespective of treatment decision (sensitivity 40.0%, specificity 70.8%), and one for when the reference standard was fluorescein angiogram graded as positive by the reading centre and the clinician recommended treatment (sensitivity 69.2%, specificity 66.2%) (see also Appendix 7, Table a). The former reference

standard was considered closer to the one used in this review and therefore it was these results that were taken to represent the study. Of 87 eyes analysed by Do et al.,[26] 15 were classed as nAMD by FFA, with 13 of the 15 CNVs described as occult with no classic. The overall prevalence of nAMD in this study was low at 17.2%. In theory prevalence should not affect sensitivity, but if the low prevalence contained more people with phenotypes that were difficult to diagnose compared with studies with a higher prevalence of disease, then this might reduce the sensitivity of the test.

By far the largest study was that by Kozak et al.[35] This retrospective study was set in the USA and involved the analysis of 1,272 eyes of 654 participants with a diagnosis of confirmed or suspected macular oedema of various aetiologies; in 541 eyes (number of participants not reported) the aetiology was nAMD. In this study, no data were presented for true negatives for the nAMD group and the total number of suspected nAMD classed by FFA as without disease was not reported; as such it was not possible to calculate specificity. The study stated that TD-OCT had detected nAMD in 13 eyes that had not been detected by FFA. As the reference standard of FFA, for the purposes of this review, was considered to have perfect sensitivity and specificity, these 13 cases were classed as TD-OCT false positive (although not shown in Figure 5 in order to prevent a spurious specificity value of 0% being calculated based on 13 false positives and zero true negatives).

Pigment epithelial detachments (PEDs) can be classified as serous (non-specific) or vascularised. The latter are characteristic of nAMD. A serous PED can occur as a result of retinal conditions other than nAMD, such as central serous chorioretinopathy, angioid streaks or others. The study by Sandhu et al.,[45] considered a serous PED to constitute presence of nAMD and on this basis reported sensitivity of 96.4% and specificity of 66.0%. However as a serous PED did not fall within our definition of nAMD for diagnostic studies, cases with serous PED were classed as non-nAMD and the data from the study were recalculated accordingly, resulting in alternative values for sensitivity of 77.8% and specificity of 76.0% and it was these values that were taken to represent this study.

Four studies, all TD-OCT,[26,39,45,48] reported both sensitivity and specificity, providing sufficient data for inclusion in a meta-analysis. One of the studies, by Talks et al.[48] was a retrospective audit on new patients referred with nAMD to a nurse-led, fast track screening clinic. Figure 6 shows a forest plot of the sensitivity and specificity of the individual studies and SROC curves for the four OCT studies. Table 5 shows the pooled estimates for the OCT studies. For all OCT studies, the pooled sensitivity and specificity (95% CI) was 88% (46% to 98%) and 78% (64% to 88%) respectively.

A likelihood ratio (LR) describes how many times a person with disease is more likely to receive a positive (LR+) or negative (LR-) test result than a person without disease. It has been suggested that positive likelihood ratios greater than 10 or negative likelihood ratios less than 0.1 can provide convincing diagnostic evidence, whilst those above 5 and less than 0.2 demonstrate strong diagnostic evidence.[53] The LR+ did not exceed 5 for OCT.

The diagnostic odds ratio (DOR) is a single summary of diagnostic performance and describes the ratio of the odds of a positive test result in an individual with disease compared to someone without disease. It has been suggested that a DOR of 25 could provide strong diagnostic evidence and that a DOR of 100 could provide convincing diagnostic evidence.[19]

Figure 6 All OCT diagnostic studies reporting sensitivity and specificity – individual study results, pooled estimates and SROC curve

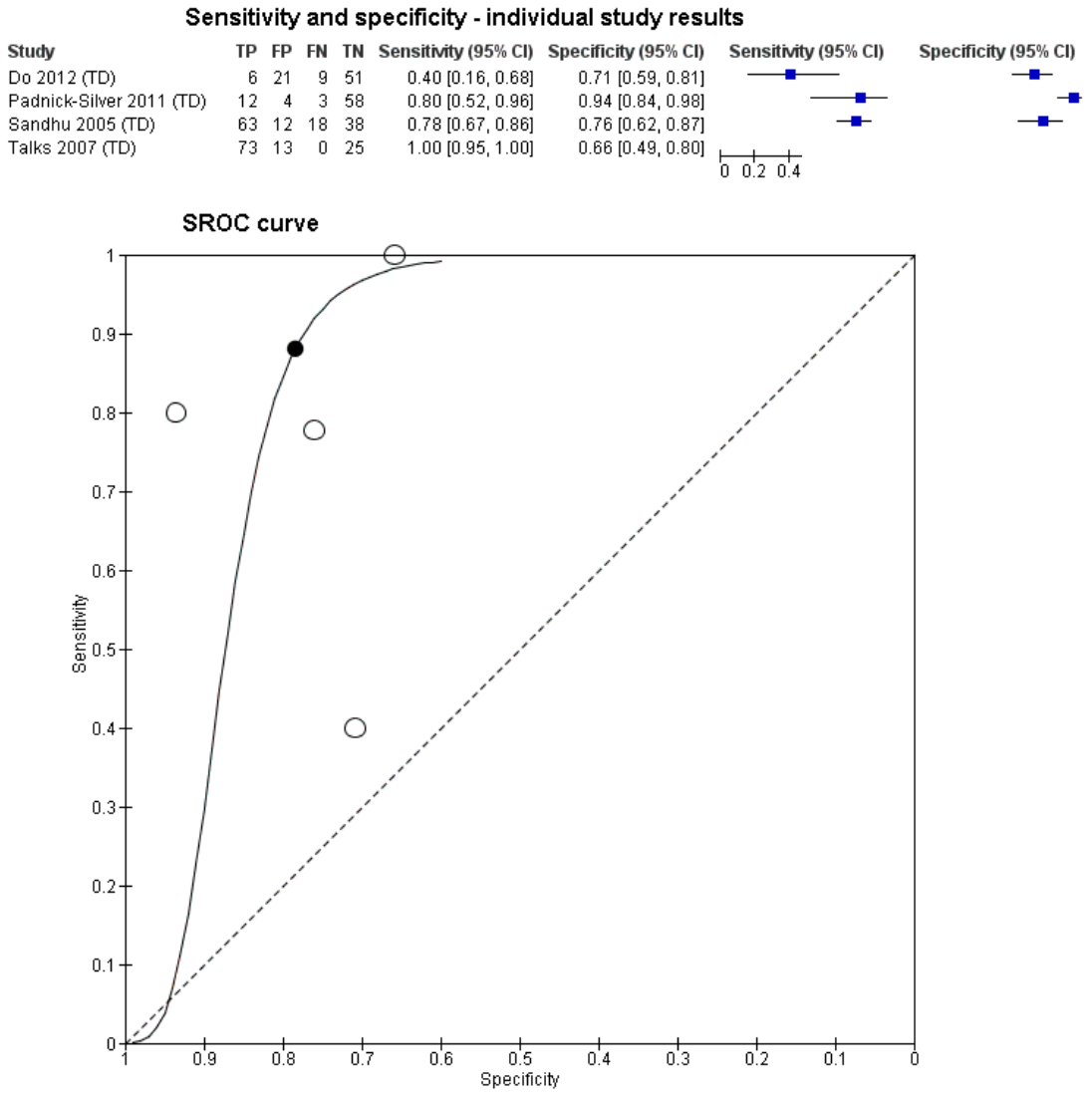


Table 5 Pooled estimates for the OCT diagnostic studies

Test	Number of studies	Number of eyes analysed	Pooled estimates (95% CI)				
			Sensitivity %	Specificity %	LR+	LR-	DOR
All OCT	4	406	88 (46 to 98)	78 (64 to 88)	4.08 (2.37 to 7.04)	0.15 (0.02 to 0.98)	26.86 (3.36 to 214.81)

Notes:

1. LR+, positive likelihood ratio; LR-, negative likelihood ratio; DOR, diagnostic odds ratio.

The risk of bias assessment of the four OCT studies included in the meta-analysis is shown in Table 6. The domains in which most studies were judged to be at high risk of bias were the patient selection domain, for reasons such as not enrolling a consecutive sample of participants,[26] not avoiding inappropriate exclusions[39] and not avoiding pre-selection of participants,[26,39,48] and the flow and timing domain, due to all patients not being included in the analysis (all four studies).

Table 6 Risk of bias of the four OCT studies included in the meta-analysis

	Risk of bias domain			
	Patient selection	**Index/ comparator test**	**Reference standard**	**Flow and timing**
Do 2012[26]	High	Low	Low	High
Padnick-Silver 2011[39]	High	Unclear	Unclear	High
Sandhu 2005[45]	Unclear	Low	Low	High
Talks 2007[48]	High	Low	High	High

Eight studies[24,32,33,36,37,40,45,48] reported the sensitivity of OCT in the detection of nAMD phenotypes (see Table 7). The studies by Cachulo et al.[24] and Khondkaryan et al.,[33] using TD-OCT, and Park et al.[40] and Talks et al.,[48] using TD-OCT, showed equally high sensitivity for the detection of each phenotype. On the other hand, the studies by Hughes et al.[32] (TD-OCT), Krebs et al.[36] (TD-OCT), Liakopoulos et al.[37] (TD-OCT) and Sandhu et al.[45] (TD-OCT) reported higher sensitivity for OCT in the detection of classic CNV compared with occult CNV.

Table 7 Sensitivity of OCT in detecting nAMD phenotypes

Study id	Test	Unit of analysis	nAMD phenotype	Number by FFA	OCT sensitivity %
Cachulo 2011[24]	TD-OCT	Eye	Predominantly classic	2	100
			Minimally classic	4	100
			Occult	6	100
			RAP	5	100
Hughes 2005[32]	TD-OCT	Eye	Classic	7	85.7
			Occult	15	13.3
Khondkaryan 2009[33]	TD-OCT	Eye	Classic	Not reported	80.9
			Occult		81.1
			RAP		57.1
Krebs 2007[36]	TD-OCT	Eye	Primarily classic	5	100
			RAP	11	72.7
Liakopoulos 2008[37]	TD-OCT	Eye	Subretinal fluid:		
			Predominantly classic	11	100
			Minimally classic	23	91.3
			Occult with no classic	24	79.2
			RAP stage III	8	50.0
			Cystoid oedema:		
			Predominantly classic	11	81.8
			Minimally classic	23	73.9
			Occult with no classic	24	58.3
			RAP stage III	8	100
Park 2010[40]	SD-OCT	Eye	Classic	7	100
			Minimally classic	3	100
			Occult	11	100
Sandhu 2005[45]	TD-OCT	Eye	Classic	56	78.6
			Occult	25	20.0
			Classic	56	82.1

	TD-OCT + fundus photo		Occult	25	12.0
Talks 2007[48]	TD-OCT	Eye	Predominantly classic	22	100
			Minimally classic	6	100
			Occult	45	100

- **Amsler Grid**

One study, by Do et al.,[26] in an analysis of 46 eyes of 46 patients, reported sensitivity of 41.7% for the Amsler Grid in detecting nAMD (specificity not reported and insufficient information to calculate prevalence of nAMD in this group). As this study also reported OCT, information on risk of bias is presented in that section.

- **Fundus autofluorescence imaging (FAF)**

One study, by Cachulo et al.,[24] in an analysis of 50 eyes of 50 patients, reported sensitivity of 93.3% and specificity of 37.1% for FAF in detecting nAMD. The prevalence of nAMD in this group was 30.0%. As this study also reported ICGA, information on risk of bias is presented in that section.

- **Colour fundus photography**

One study, by Alster et al.,[23] in an analysis of 120 eyes of 120 patients, reported sensitivity of 70.0% and specificity of 95.0% for colour fundus photography in detecting nAMD. The prevalence of nAMD in this study was 53.3%. As this study also reported PHP, information on risk of bias is presented in that section.

- **Preferential hyperacuity perimetry (PHP)**

Three studies analysing 302 eyes of 302 patients reported the diagnostic accuracy of the PHP test in detecting nAMD.[23,26,38] Figure 7 shows a forest plot with the individual study results for sensitivity and specificity. The studies by Alster et al.[23] and Loewenstein et al.[38] reported similarly high sensitivity and specificity. However it was not possible to calculate pooled estimates using HSROC methodology due to insufficient data. The study by Do et al.[26] reported lower sensitivity and did not report specificity. Across the studies the median (range) of sensitivity values reported was 82% (50% to 85%). The specificity values reported by Alster et al.[23] and Loewenstein et al.[38] were 88% and 85% respectively.

Across the three studies, the median (range) prevalence of nAMD was 50.4% (17.2% to 53.3%).

The risk of bias assessment of the three PHP studies is shown in Table 8. The domains in which most studies were judged to be at high risk of bias were the patient selection domain, for reasons such as inappropriate exclusions[23,38] and pre-selection of participants,[23,26,38] and the flow and timing domain, for reasons such as an interval of more than one week between the index test and reference standard,[23,38] not all patients receiving the reference standard test[38] and not all patients included in the analysis.[23,38]

Figure 7 PHP studies – individual study results for sensitivity and specificity

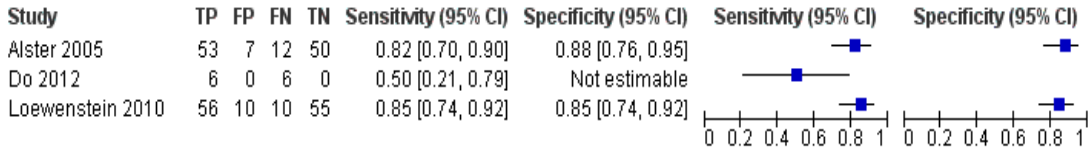


Table 8 Risk of bias of the PHP studies

	Risk of bias domain			
	Patient selection	**Index/ comparator test**	**Reference standard**	**Flow and timing**
Alster 2005[23]	High	Low	Low	High
Do 2012[26]	High	Low	Low	High
Loewenstein 2010[38]	High	Unclear	Unclear	High

Loewenstein et al.[38] also reported the ability of PHP in detecting nAMD phenotypes, with 90% (18/20) sensitivity for minimally or predominantly classic CNV and 82.6% (38/46) sensitivity for occult CNV.

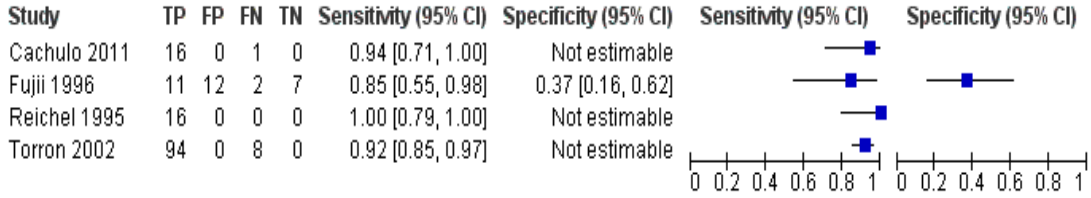
- **Indocyanine green angiography (ICGA)**

Eight studies reported the diagnostic accuracy of ICGA in detecting nAMD, of which seven[24,25,28,30,43,47,50] reported the eye as the unit of analysis and one[41] reported the patient as the unit of analysis. Four of these studies only reported detection of nAMD phenotypes: IPCV;[30] occult CNV;[25] type 2 CNV without an occult component;[47] and RAP.[41]

The median (range) prevalence of nAMD across three studies where this information was available at participant level (and excluding studies reporting results only at phenotype level) was 80.0% (32.7% to 100%).[24,43,50]

Figure 8 shows a forest plot of the sensitivity and specificity of the individual studies (excluding the four that only reported detection of phenotypes). Across the studies the median (range) sensitivity reported was high at 93% (85% to 100%). Only the study by Fujii et al.[28] reported specificity, which was low at 37%.

Figure 8 ICGA sensitivity and specificity – individual study results



In the study by Reichel et al.[43] all participants were deemed to have nAMD (therefore there could be no true negatives and it was not possible to calculate specificity). Only participants who were suspected to have a CNV obscured by haemorrhage were included in this study. The authors stated that ICGA had detected nAMD in four eyes that had not been detected by FFA. As the reference standard of FFA, for the purposes of this review, was considered to have perfect sensitivity and specificity, these four cases were classed as ICGA false positives (although not shown in Figure 8 in order to prevent a spurious specificity value of 0% being calculated based on four false positives and zero true negatives).

The risk of bias assessment of the four ICGA studies is shown in Table 9. The domains in which most studies were judged to be at high risk of bias were the index/comparator test domain, due to the ICGA test being interpreted with knowledge of the FFA results, and the reference standard domain, due to FFA being interpreted with knowledge of the ICGA results.[43,50]

Table 9 Risk of bias of the four ICGA studies included in the forest plot

	Risk of bias domain			
	Patient selection	**Index/ comparator test**	**Reference standard**	**Flow and timing**
Cachulo 2011[24]	Unclear	Unclear	Unclear	High
Fujii 1996[28]	Unclear	Unclear	Unclear	Unclear
Reichel 1995[43]	High	High	High	Low
Torron 2002[50]	Unclear	High	High	Unclear

Four studies[25,30,41,47] reported the sensitivity of ICGA in the detection of nAMD phenotypes, with each study reporting detection of a different phenotype (see Table 10). Sensitivity was 100% for detection of IPCV[30] and type 2 CNV without an occult component,[47] high (85.1%) for detection of RAP[41] but lower (62.9%) for detection of occult CNV.[25]

Table 10 Sensitivity of ICGA in detecting nAMD phenotypes

Study id	Test	Unit of analysis	nAMD phenotype	Number by FFA	ICGA sensitivity %
Chen 2003[25]	ICGA	Eye	Occult CNV	35	62.9
Gomi 2007[30]	ICGA	Eye	IPCV	37	100
Sulzbacher 2011[47]	ICGA	Eye	Type 2 CNV without an occult component	13	100
Parravano 2012[41]	ICGA	Patient	RAP	155	85.1

Studies directly comparing tests

- **PHP versus colour fundus photography versus colour fundus photography plus visual acuity**

One study, by Alster et al.,[23] analysing one eye per patient, reported PHP (n=122 eyes) compared with colour fundus photography (n=120 eyes) and colour fundus photography plus visual acuity (n=66 eyes). Sensitivity was highest for PHP (81.5%), followed by colour fundus photography (70.0%) and lowest for colour fundus photography plus visual acuity (53.0%). Specificity was similarly high for colour fundus photography (95.0%) and colour fundus photography plus visual acuity (94.0%), followed by PHP (87.7%).

- **TD-OCT versus ICGA versus fundus autofluorescence imaging (FAF)**

One study, by Cachulo et al.,[24] analysing one eye per patient, reported TD-OCT (n=52 eyes) compared with ICGA (n=52 eyes) and FAF (n=50 eyes). Sensitivity was high for all three tests (TD-OCT 100%, ICGA 94.1%, FAF 93.3%). Specificity was only reported for FAF, which was low at 37.1%.

- **TD-OCT versus Amsler grid versus PHP**

One study, by Do et al.,[26] analysing one eye per patient, reported TD-OCT (n=87 eyes) compared with Amsler grid (n=46 eyes) and PHP (n=49 eyes). Based on the set of results for CNV defined as positive by FFA irrespective of the treatment decision, the sensitivity for all three tests was fairly low (PHP 50.0%, Amsler grid 41.7%, TD-OCT 40.0%). Specificity was only reported for TD-OCT, which was moderate at 70.8%. As previously stated, the overall

prevalence of nAMD in this study was low at 17.2%, the majority of which were occult CNV, which might at least partly explain the low sensitivity reported by this study for TD-OCT.

- **TD-OCT versus TD-OCT plus stereo colour fundus photography**

One study, by Sandhu et al.,[45] reported TD-OCT compared with TD-OCT plus stereo colour fundus photography (both n=131 eyes of 118 participants). As previously stated, serous PED did not fall within this review's definition of nAMD for diagnostic studies and the study data were recalculated accordingly. Based on the recalculated data, sensitivity was similar and moderately high for both tests (TD-OCT 77.8%, TD OCT plus stereo colour fundus photography 74.1%) while specificity was higher for the combination (92.0%) than for TD-OCT alone (76.0%).

Studies reporting combinations of tests

Two studies reported combinations of tests. Sandhu et al.[45] reported TD-OCT combined with stereo colour fundus photography. Alster et al.[23] reported colour fundus photography combined with visual acuity. As both studies also reported other tests, the results for the test combinations are included in the preceding section on studies directly comparing tests.

Assessment of other outcomes of interest

- **Clinical effectiveness**

No studies were identified that met our inclusion criteria of providing information on clinical effectiveness outcomes (e.g. visual acuity) when treatment was based on OCT compared with FFA findings.

- **Interpretability of the tests**

Six diagnostic studies[23,24,26,35,38,45] provided information relating to the interpretability of the tests, inasmuch as they reported on the numbers excluded from analysis due to poor image quality (see Table 11). In the TD-OCT study by Do et al.,[26] 166 individuals were screened and 98 were enrolled; in six of the 68 individuals screened but not enrolled the reason given was poor image quality. However it was unclear whether the excluded images related to OCT, colour fundus photography or FFA. In the TD-OCT study by Sandhu et al.,[45] 10/128 individuals (7.8%) were excluded from the analysis due to poor image quality. It was also unclear in this study whether the excluded images related to OCT or FFA.

Table 11 Studies reporting numbers excluded from analysis due to poor image quality

Study id	Test	Excluded from analysis, n (%)	Reason
Alster 2005[23]	PHP	11/185 (5.9%) individuals/eyes	Results judged to be unreliable
	Colour fundus photography	17/185 (9.2%) individuals/eyes	Inadequate or poor quality photographs
Cachulo 2011[24]	FAF	2/52 (3.8%) individuals/eyes	Pattern of autofluorescence could not be determined
Do 2012[26]	TD-OCT, PHP, Amsler Grid, colour fundus photography	6/104 (5.8%) individuals/eyes	Poor image quality that was insufficient to permit successful participation
Kozak 2008[35]	TD-OCT	35/1307 (2.7%) eyes	Poor quality or image decentration
Loewenstein 2010[38]	PHP, colour fundus photography	40/208 (19.2%) individuals/eyes	Geographic atrophy, early AMD, pattern dystrophy, no or poor-quality photographs
Sandhu 2005[45]	TD-OCT	10/128 (7.8%) individuals	Poor quality of the images

Notes:

1. In the study by Do et al.,[26] 166 individuals were screened for study participation, of whom 98 were enrolled. Of the 68 individuals screened but not enrolled, the reason for this in 6 was poor image quality. Our calculation of 5.8% excluded from the analysis was based on 6 as a percentage of 104 (98 + 6), on the assumption that these 6 individuals would have been enrolled had their images been of sufficient quality.
2. In the study by Kozak et al.,[35] of 1272 eyes analysed, 541 were nAMD with the remainder macular oedema due to other aetiologies. 35 eyes were excluded prior to analysis due to poor quality or image decentration, but it was not reported how many of these specifically related to nAMD.
3. In the study by Loewenstein et al.,[38] the specific number of individuals excluded solely due to poor quality photographs was not reported.

- **Acceptability of the tests**

No studies were identified meeting our inclusion criteria that reported the acceptability of the tests, either to those providing the tests or to those receiving them.

- **Proportion of participants unable to receive the diagnostic test**

Ten studies reported exclusion criteria relating to eye conditions (see Appendix 8, Table a).[23,24,26,30,38-40,43,47,48] The studies detailed various eye-related exclusion criteria, for example evidence of macular disease other than AMD, previous surgical or laser treatment within the macular area, presence of any significant media opacity that precluded a clear view of the fundus, subretinal or subpigment epithelial haemorrhages that obscured lesions, and recent ocular surgery in the study eye.

A few non-ophthalmic exclusion criteria were reported including current or past history of a medical condition that would preclude scheduled study visits or completion of the study,[24] allergy to fluorescein dye[26] and allergy to iodine-based dye.[43] In the PHP study by Loewenstein et al.,[38] individuals with no experience of using a computer mouse were taught how to use the mouse and participation in the study was conditional on passing an in-house computer mouse tutorial. The authors reported that 15 people did not pass the tutorial and were excluded from the study.

- **Other health professionals compared with ophthalmologists interpreting OCT findings**

No studies were identified meeting our inclusion criteria that reported the performance of other health professionals compared with ophthalmologists in interpreting OCT findings. The setting for the TD-OCT study by Talks et al.[48] was a nurse-led, fast-track screening clinic in the UK for new nAMD referrals but did not involve a comparison with other health professionals in interpreting OCT findings. Trained nurses and an ophthalmic photographer, who consulted an ophthalmologist when in doubt, conducted the screening visit. If the visual acuity was ≥ 6/60 an OCT was performed. If dry AMD or other retinal pathology was seen, the patient was referred for management appropriate to their condition but no further imaging was performed. The remaining patients underwent simultaneous FFA and ICGA. The images were taken, using standard protocols, by an ophthalmic photographer. The ophthalmologist reviewed the images the following day.[48]

6.3 Assessment of monitoring studies

6.3.1 Characteristics of the included monitoring studies

Appendix 5 (Table b) provides details of the individual study characteristics for the eight monitoring studies. Table 12 provides summary information for the studies. Of the eight monitoring studies, four were prospective,[31,42,44,52] three were retrospective[15,27,29] while in the study by van de Moere et al.[51] this information was not reported. In five studies the participants were a consecutive sample.[27,29,42,44,52] The eight studies enrolled 463 participants.

Five studies used the eye as the unit of analysis (363 eyes),[15,27,29,51,52] while three used test examination as the unit of analysis (61 pairs of OCT and FFA examinations,[31] 176 pairs of OCT and FFA examinations[44] and 54 pairs of ICGA and FFA examinations).[42]

Table 12 Summary of the characteristics of the included monitoring studies

Characteristic	Number	Number of studies
Participants enrolled	463	8
Analysed (eyes)	363	5
Analysed (examinations, pairs)	291	3
Age: Median (range) of means/medians	76.5 (73.9 to 78.1)	7
Gender: male: female n (%)	177 (46.8%): 201 (53.2%)	6
Median (range) prevalence of nAMD	57.9% (49.2% to 83.3%)	5
Tests reported (number enrolled)		
OCT	442	7
TD-OCT	349	6
SD-OCT	152	2
ICGA	21	1
Type of treatment received		
Anti-VEGF	149	2
PDT	293	5
Laser photocoagulation	21	1

Notes:

1. Anti-VEGF, anti-vascular endothelial growth factor; ICGA, indocyanine green angiography; nAMD, neovascular age-related macular degeneration; OCT, optical

coherence tomography; PDT, photodynamic therapy; TD-OCT, time domain optical coherence tomography; SD-OCT, spectral domain optical coherence tomography.

2. The median (range) prevalence of active nAMD was derived from five studies where this information was available at participant level. Three studies reporting examination as the unit of analysis, where it was not possible to ascertain the number of participants with nAMD, were not included in these calculations.[31,42,44]
3. One study reported both TD-OCT and SD-OCT.[15]

Two studies were undertaken in the USA[15,42] and one each in Italy,[29] Germany,[31] the Netherlands,[52] Spain[44] and the UK (Royal Victoria Infirmary, Newcastle upon Tyne).[51] One study was international, taking place in two centres in the USA and Germany.[27]

The largest study was by van de Moere et al.,[51] which reported TD-OCT, was set in the UK and analysed 121 eyes, while the smallest was by van Velthoven et al.,[52] reporting TD-OCT and analysing 30 eyes.

Across seven studies[15,27,29,42,44,51,52] reporting the mean or median age of the participants the median (range) of these values was 76.5 years (73.9 to 78.1 years). Six studies involving 378 participants provided information on gender,[27,29,42,44,51,52] in which 177 (46.8%) participants were men and 201 (53.2%) women. The median (range) prevalence of active nAMD across five studies where this information was available at participant level was 57.9% (49.2% to 83.3%).[15,27,29,51,52]

Seven studies reported OCT (six TD-OCT;[15,27,31,44,51,52] and two SD-OCT).[15,29,44,51] (The study by Khurana et al.[15] reported both TD-OCT and SD-OCT.) One study, by Regillo et al.,[42] reported ICGA.

Of the seven studies reporting OCT, five used the eye as the unit of analysis (number of eyes analysed = 363).[15,27,29,51,52] In four of these studies one eye per patient was analysed (n = 304 eyes).[27,29,51,52] Two studies reported examination as the unit of analysis (both TD-OCT).[31,44] Two studies reported detection of nAMD phenotype activity: classic and occult CNV;[29] and pigment epithelial detachment (PED) and cystoid macular oedema.[51] The studies by Henschel et al.[31] and van de Moere et al.[51] also reported the performance of OCT in detecting intraretinal and subretinal fluid.

In two OCT monitoring studies[15,29] the participants had received anti-vascular endothelial growth factor (anti-VEGF) therapy while in five[27,31,44,51,52] the treatment was photodynamic

therapy (PDT). In the study reporting ICGA[42] the participants had received laser photocoagulation treatment.

6.3.2 Risk of bias of the included monitoring studies

Figure 9 presents a summary of the results for the QUADAS-2 risk of bias and applicability domains across the eight full-text monitoring papers. Appendix 6 (Table b) presents the results of the risk of bias and applicability concerns for the individual studies.

No study was judged to have a low risk of bias across all domains. More studies in the patient selection domain (n = 2, 25%) and the flow and timing domain (n = 2, 25%) were judged to be at high risk of bias than in the index/comparator test domain (n = 1, 12.5%) and reference standard domain (n = 1, 12.5%).

In the patient selection domain three studies[42,51,52] (37.5%) were judged to be at low risk of bias, while two[29,44] (25%) were considered to have a high risk of bias and in three[15,27,31] (37.5%) the risk of bias was unclear. The study by Giani et al.[29] was judged to be at high risk of bias due to not avoiding inappropriate exclusions and pre-selection of participants, while the study by Salinas-Alaman et al.[44] was judged to be at high risk of bias due to not avoiding pre-selection of participants.

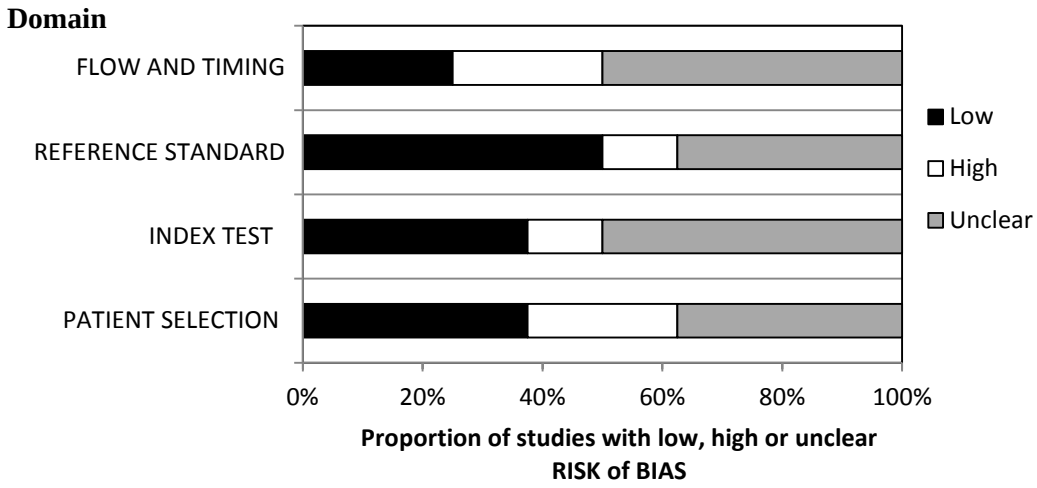
In the index/comparator test domain three studies (37.5%) were judged to be at low risk of bias,[27,29,31] one (12.5%) was considered high risk of bias[42] while in the remaining four (50%) the risk of bias was considered to be unclear.[15,44,51,52] The reasons for the study by Regillo et al.[42] being judged to be at high risk of bias was that the test (ICGA) was interpreted with knowledge of the results of the reference standard.

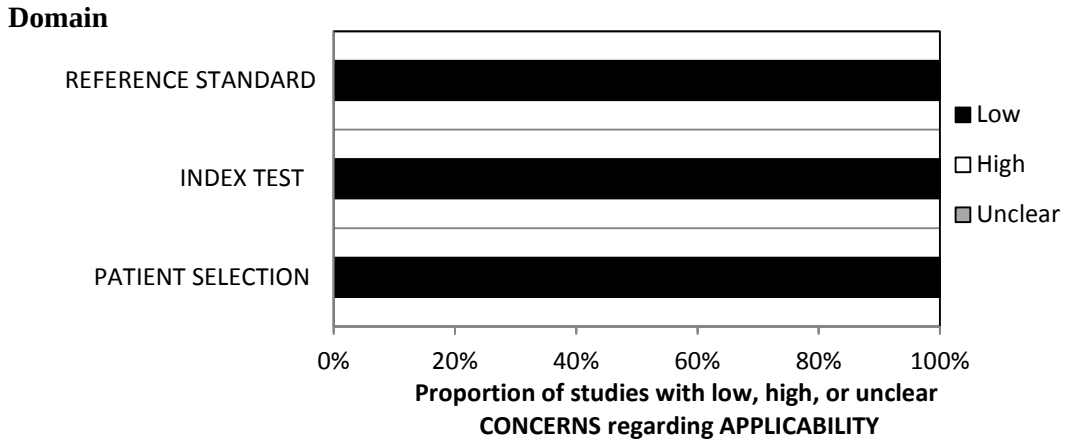
In the reference standard domain four studies (50%) were judged to be at low risk of bias,[27,29,31,52] one (12.5%) was considered high risk of bias[42] while in the remaining three (37.5%) the risk of bias was considered to be unclear.[15,44,51] The Regillo et al.[42] study was judged to be at high risk of bias as the reference standard test was interpreted with knowledge of the results of the comparator test (ICGA).

In the flow and timing domain two studies (25%) were judged to be at low risk of bias,[15,42] two[44,51] (25%) were considered to have a high risk of bias while in the remaining four[27,29,31,52] (50%) the risk of bias was considered to be unclear. The studies by Khurana et al.[15] and Regillo et al.[42] were judged to be at high risk of bias as not all patients were included in the analysis.

All eight studies were judged to have low concerns for applicability on the patient selection, index/comparator test, and reference standard domains.

Figure 9 Summary of risk of bias and applicability domains (monitoring studies)





6.3.3 Results – detection of active nAMD

Individual study results are presented in Appendix 7 (Table b).

Single tests

- **OCT**

Seven studies reported the accuracy of OCT in detecting active nAMD, of which five reported TD-OCT,[27,27,31,31,44,51,52,52] one reported SD-OCT[29,44,51] and one reported both TD-OCT and SD-

OCT.[15] In five studies the unit of analysis was the eye[15,27,29,51,52] while in two the unit of analysis was pairs of OCT and FFA examinations.[31,44]

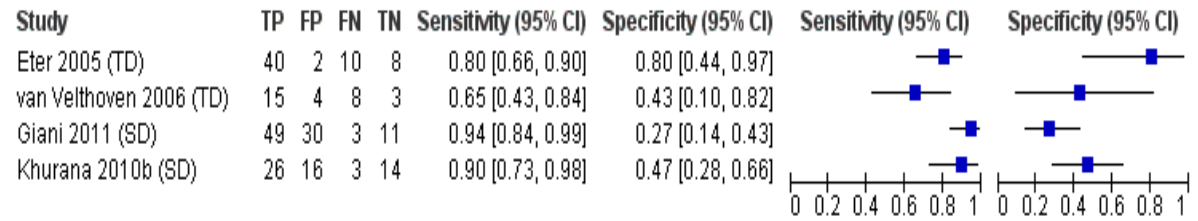
The median (range) prevalence of active nAMD across five studies where this information was available at participant level was 57.9% (49.2% to 83.3%).[15,27,29,51,52]

Three TD-OCT studies[15,27,52] and two SD-OCT studies,[15,29] with eye as the unit of analysis, reported both sensitivity and specificity, providing sufficient data for inclusion in a meta-analysis. Figure 10 shows forest plots of the sensitivity and specificity of the individual studies and SROC curves for (a) all of the OCT studies, (b) the three TD-OCT studies and (c) the two SD-OCT studies respectively. Table 13 shows the pooled estimates for these studies. As the study by Khurana et al.[15] reported both TD-OCT and SD-OCT for the same 59 eyes, we chose to display only the data for SD-OCT from this study in the forest plot of all OCT studies and to include only the SD-OCT data from this study in the pooled estimates for all OCT studies, in order to avoid double counting and on the basis that the SD-OCT data were the more appropriate to include in the pooled estimates for all OCT. The TD-OCT data from Khurana et al.[15] are included in the forest plot and SROC curve for TD-OCT in Figure 10 and were included in the pooled estimates for TD-OCT shown in Table 13. For all OCT studies, the pooled sensitivity and specificity (95% CI) was 85% (72% to 93%) and 48% (30% to 67%) respectively. For TD-OCT, the pooled sensitivity and specificity (95% CI) was 70% (56% to 80%) and 65% (48% to 79%). For both TD-OCT and the group of all four OCT studies the likelihood ratio and DOR values reported were below the level suggestive of strong diagnostic evidence.

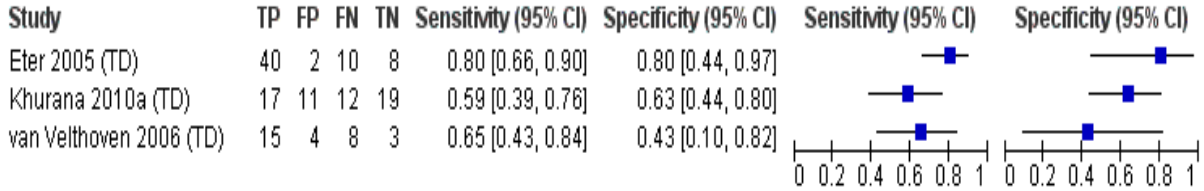
It was not possible to calculate pooled estimates using HSROC methodology for the two SD-OCT studies due to insufficient data. These studies reported sensitivities of 94%[29] and 90%[15] and specificities of 27%[29] and 47%,[15] which suggests that SD-OCT has higher sensitivity than TD-OCT but lower specificity. In order to provide a pooled estimate using HSROC methodology for SD-OCT monitoring for the economic model a third study, by Salinas-Alaman et al.,[44] using examination as the unit of analysis (n=176), was included along with those of Giani et al[29] and Khurana et al.[15] This resulted in pooled sensitivity and specificity (95% CI) of 94% (90% to 97%) and 44% (29% to 61%) respectively.

Figure 10 OCT monitoring studies reporting sensitivity and specificity for detection of nAMD activity – individual study results and SROC curves

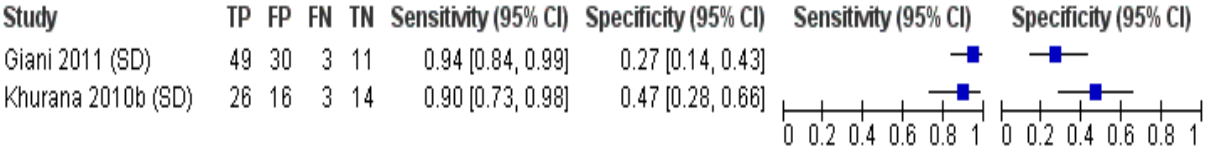
Sensitivity and specificity – individual study results – all OCT



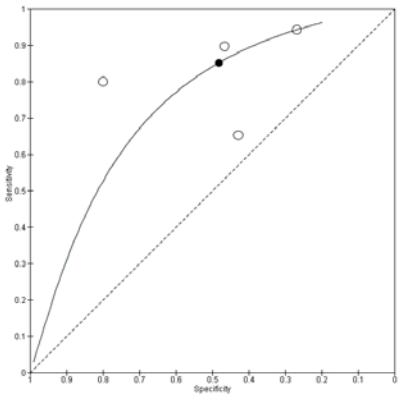
Sensitivity and specificity – individual study results – TD-OCT



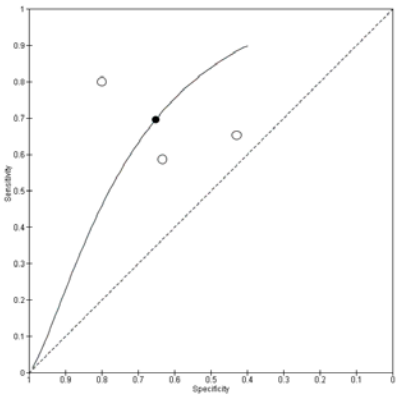
Sensitivity and specificity – individual study results – SD-OCT



SROC curve – all OCT



SROC curve – TD-OCT



SROC curve – SD-OCT

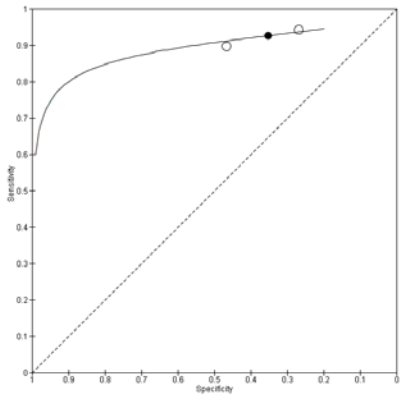


Table 13 Pooled estimates for the OCT monitoring studies

Test	Number of studies	Number of eyes analysed	Pooled estimates (95% CI)				
			Sensitivity %	Specificity %	LR+	LR-	DOR
All OCT	4	242	85 (72 to 93)	48 (30 to 67)	1.64 (1.19 to 2.26)	0.31 (0.18 to 0.54)	5.33 (2.57 to 11.06)
TD-OCT	3	149	70 (56 to 80)	65 (48 to 79)	2.00 (1.19 to 3.36)	0.47 (0.28 to 0.78)	4.27 (1.58 to 11.53)
SD-OCT	2	152	Not calculable using HSROC methodology				

Notes:

1. Khurana et al.[15] reported both TD-OCT and SD-OCT for the same 59 eyes of 56 patients analysed; only the SD-OCT data were included in the pooled estimates for 'All OCT' in order to avoid double counting.

The risk of bias assessment of the four OCT studies included in the meta-analysis is shown in Table 14. The only judgement of high risk of bias was for the study by Giani et al.[29] for the patient selection domain (inappropriate exclusions and pre-selection of participants).

Table 14 Risk of bias of the four OCT studies included in the meta-analysis

	Risk of bias domain			
	Patient selection	**Index/ comparator test**	**Reference standard**	**Flow and timing**
Eter 2005[27]	Unclear	Low	Low	Unclear
Giani 2011[29]	High	Low	Low	Unclear
Khurana 2010[15]	Unclear	Unclear	Unclear	Low
Van Velthoven 2006[52]	Low	Unclear	Low	Unclear

Two studies used examination as the unit of analysis. Henschel et al.,[31] in an analysis of 61 pairs of TD-OCT and FFA examinations from 14 patients, reported sensitivity of 96.8% and specificity of 36.7% for CNV based on detection of intraretinal and/or subretinal fluid. Salinas-Alaman et al.,[44] in an analysis of 176 pairs of TD-OCT and FFA examinations (number of patients not stated), reported sensitivity of 95.7% and specificity of 59.0% based on detection of intraretinal or subretinal fluid.

Four studies[15,29,31,51] reported the sensitivity of OCT in detecting active nAMD phenotypes or active nAMD based on detection of intraretinal/subretinal fluid (see Table 15). The study by Giani et al.[29] reported high sensitivity for the detection by SD-OCT of both classic and occult CNV activity (90.9% and 100% respectively). In the studies by Henschel et al.[31] (unit of analysis: examination) and van de Moere et al.[51] (unit of analysis: eye) sensitivity was higher for nAMD activity based on detection of intraretinal fluid (90.3% and 82.9% respectively) compared with subretinal fluid (71.0% and 47.1% respectively). Van de Moere et al.[51] also reported sensitivity of TD-OCT for detection of cystoid macular oedema and pigment epithelial detachment, both low at 22.9% and 5.7% respectively. In the study by Khurana et al[15] the sensitivity of SD-OCT was higher than that of TD-OCT for nAMD activity based on the detection of intraretinal fluid, retinal cystoid abnormalities or subretinal fluid.

Table 15 Sensitivity of OCT in detecting nAMD phenotype activity

	Unit of analysis	Detection of	Number by FFA	OCT sensitivity %
Giani 2011[29] (SD-OCT)	Eye	Classic CNV	57	90.9
		Occult CNV	36	100
Khurana 2010[15] (TD-OCT)	Eye	Intraretinal fluid	29	37.9
		Retinal cystoid abnormalities	29	34.5
		Subretinal fluid	29	48.3
Khurana 2010[15] (SD-OCT)	Eye	Intraretinal fluid	29	65.5
		Retinal cystoid abnormalities	29	58.6
		Subretinal fluid	29	69.0
Van de Moere 2006 [51] (TD-OCT)	Eye	Intraretinal fluid	Not reported	82.9
		Subretinal fluid		47.1
		CMO		22.9
		PED		5.7
Henschel 2009 [31] (TD-OCT)	Exam	Intraretinal fluid	31	90.3
		Subretinal fluid	31	71.0

Notes:

1. CMO, cystoid macular oedema; PED, pigment epithelial detachment.

- **ICGA**

One study, by Regillo et al.,[42] in an analysis of 54 pairs of indocyanine green angiograms compared with fluorescein angiograms, obtained from 24 eyes of 21 patients, reported sensitivity of 75.9% and specificity of 88.0% in detecting nAMD activity. It was not possible to ascertain (at participant-level) the prevalence of nAMD. This study was judged as high risk of bias for the index/comparator test, and reference standard, domains, due to the ICGA-FFA pairs being analysed directly from the computer monitor (ICGA test results interpreted with knowledge of the FFA results, and vice versa) and low risk of bias for the other domains.

Studies directly comparing tests

- **TD-OCT versus SD-OCT**

One study, by Khurana et al.,[15] compared TD-OCT with SD-OCT in an analysis of 59 eyes of 56 participants. Although sensitivity was considerably higher for SD-OCT than for TD-OCT (89.7% versus 58.6%), specificity was lower (46.7% versus 63.3%).

6.3.4 Assessment of other outcomes of interest

- **Clinical effectiveness**

No studies were identified that met our inclusion criteria providing information on clinical effectiveness outcomes (e.g. visual acuity) when treatment was based on OCT compared with FFA findings.

- **Interpretability of the tests**

Only one monitoring study, by van de Moere et al.,[51] reported information relating to the interpretability of the tests. This TD-OCT study reported that, of 136 participants enrolled, 17 (12.5%) were excluded from the analysis due to the poor quality of the OCT or FFA images. The study did not specify how many of these poor quality images were OCT images and how many were FFA.

- **Acceptability of the tests**

No studies were identified that met our inclusion criteria reporting the acceptability of the tests, either to those providing the tests or to those receiving them.

- **Proportion of participants unable to receive the monitoring test**

Two studies reported exclusion criteria relating to eye conditions (see Appendix 8, Table b).[15,29] The study by Giani et al.[29] contained the following exclusion criteria: any previous laser treatment, photodynamic therapy, or vitreoretinal surgery on the study eye; significant macular

haemorrhage that obscured the lesion; and a spherical refractive error > 6 diopters. The study by Khurana et al.[15] excluded patients with CNV resulting from causes other than AMD.

- **Other health professionals compared with ophthalmologists interpreting OCT findings**

No studies were identified meeting our inclusion criteria that reported the performance of other health professionals compared with ophthalmologists in interpreting OCT findings.

6.4 Summary of the reviews of diagnostic and monitoring studies

6.4.1 Diagnostic studies

Twenty-two diagnostic studies were included (20 full-text papers, two abstracts). The full-text papers were assessed for risk of bias using the QUADAS-2 checklist. The domains in which the greatest number were judged to be at high risk of bias were the patient selection domain (55%, 11/20), for reasons such as inappropriate exclusions and pre-selection of participants, and flow and timing domain (40%, 8/20), for reasons such as the length of time between the index test and the reference standard, and not all participants being included in the analysis. The risk of bias in the index/comparator test and reference standard domains was judged to be unclear in 50% (10/20) and 60% (12/20) of studies respectively. All of the studies were judged to have low concerns in terms of their applicability to the question being addressed by the review.

A descriptive summary of the results of the diagnostic studies with eye as the unit of analysis is shown in Table 16 (excluding studies that only reported detection at phenotype level). Across the studies the median (range) sensitivity was high for OCT (94.5%, range 36.0% to 100%; ten studies. Sensitivity was also high for ICGA (93.2%, range 84.6% to 100%; four studies) and FAF (93.3%; one study), followed by PHP (81.5%, range 50.0% to 84.8%; three studies), colour fundus photography 70.0%; one study) and lowest for Amsler Grid (41.7%; one study). The median (range) specificity for OCT was moderate (73.5%, range 65.8% to 93.5%; four studies). Specificity was highest for colour fundus photography (95%; one study), followed by PHP (84.6% and 87.7%; two studies), and was low for FAF (37.1%; one study) and ICGA (36.8%; one study).

Two studies reported the diagnostic accuracy of combinations of tests. Sensitivity and specificity for TD-OCT plus colour fundus photography was 74.1% and 92.0% respectively, while for colour fundus photography plus visual acuity sensitivity was lower at 53.0% but with similarly high specificity at 94.0%.

Table 16 Descriptive summary of sensitivity and specificity of diagnostic studies

Test	No. of studies	No. of eyes analysed	Median (range) sensitivity %	Median (range) specificity %
All OCT	10	1117	94.5 (36 to 100)	73.4 (66 to 94)
TD-OCT	9	1096	92.3 (36 to 100)	73.4 (66 to 94)
SD-OCT	1	21	100.0	Not reported
Amsler Grid	1	46	41.7	Not reported
PHP	3	302	81.5 (50.0 to 84.8)	(84.6, 87.7)
Colour fundus photography	1	120	70.0	95.0
FAF	1	50	93.3	37.1
ICGA	4	167	93.2 (84.6 to 100)	36.8
TD-OCT + colour fundus photography	1	131	74.1	92.0
Colour fundus photography + visual acuity	1	66	53.0	94.0

Four OCT diagnostic studies (all TD-OCT) provided sufficient data for inclusion in a meta-analysis (see Table 17). The pooled sensitivity and specificity (95% CI) for all four OCT studies was 88% (46% to 98%) and 78% (64% to 88%) respectively.

Table 17 Pooled estimates for the OCT diagnostic studies

Test	No. of studies	No. of eyes analysed	Pooled estimates (95% CI)	
			Sensitivity %	Specificity %
All OCT	4	406	88 (46 to 98)	78 (64 to 88)

Eight diagnostic studies reported the sensitivity of OCT in the detection of specific nAMD phenotypes. Four showed equally high sensitivity for the detection of each phenotype. In four others sensitivity for OCT was higher in the detection of classic CNV (range 79% to 100%) compared with occult CNV (range 13% to 79%). Four studies reported the sensitivity of ICGA in the detection of specific nAMD phenotypes. Each study reported detection of a different phenotype, with 100% sensitivity for detection of IPCV and type 2 CNV without an occult component, high sensitivity (85.1%) for detection of RAP but lower sensitivity (62.9%) for detection of occult CNV.

6.4.2 Monitoring studies

Eight monitoring studies were included (all full-text papers). Seven reported OCT, six with eye as the unit of analysis (one of which only reported detection at phenotype level) and two with test examination as the unit of analysis. One study reported ICGA. As with the diagnostic studies, the QUADAS-2 domains in which the greatest number of monitoring studies were judged to be at high risk of bias were the patient selection domain (25%, 2/8), for reasons such as inappropriate exclusions and pre-selection of participants, and flow and timing domain (25%, 2/8), for reasons such as the length of time between the index test and the reference standard, and not all participants being included in the analysis. The risk of bias in the index/comparator test and reference standard domains was judged to be unclear in 50% (4/8) and 37.5% (3/8) of studies respectively. All of the monitoring studies were judged to have low concerns in terms of their applicability to the question being addressed by the review.

Four OCT monitoring studies, with eye as the unit of analysis, provided sufficient data for inclusion in a meta-analysis (see Table 18). The pooled sensitivity and specificity (95% CI) for all four OCT studies was 85% (72% to 93%) and 48% (30% to 67%) respectively. For TD-OCT, the pooled sensitivity and specificity was 70% (56% to 80%) and 65% (48% to 79%). It was not possible to calculate pooled estimates using HSROC methodology for the two SD-OCT studies due to insufficient data. These two studies reported sensitivities of 94% and 90% and specificities of 27% and 47%, which, similar to the diagnostic studies, suggests that SD-OCT has higher sensitivity than TD-OCT but lower specificity.

Table 18 Pooled estimates for the OCT monitoring studies

Test	No. of studies	No. of eyes analysed	Pooled estimates (95% CI)	
			Sensitivity %	Specificity %
All OCT	4	242	85 (72 to 93)	48 (30 to 67)
TD-OCT	3	149	70 (56 to 80)	65 (48 to 79)
SD-OCT	2	152	Not calculable using HSROC methods	

Notes:

1. Three studies reported TD-OCT and two studies reported SD-OCT, with one study reporting both TD-OCT and SD-OCT. Only the data for SD-OCT from this study were included in the pooled estimates for all OCT to avoid double counting.

Two OCT monitoring studies used test examination as the unit of analysis. The first, in an analysis of 61 pairs of TD-OCT and FFA examinations from 14 patients, reported high sensitivity of 96.8% but low specificity of 36.7%, for CNV based on detection of intraretinal and/or subretinal fluid. The second, in an analysis of 176 pairs of SD-OCT and FFA examinations (number of patients not stated), reported similarly high sensitivity of 95.7% and moderate specificity of 59.0% based on detection of intraretinal or subretinal fluid.

One ICGA monitoring study used test examination as the unit of analysis. In an analysis of 54 pairs of indocyanine green angiograms compared with fluorescein angiograms, obtained from 24 eyes of 21 patients, sensitivity of 75.9% and specificity of 88.0% was reported for detecting nAMD activity.

Three studies reported OCT sensitivity in detecting activity of specific nAMD phenotypes or nAMD activity based on detection of intraretinal/subretinal fluid. SD-OCT sensitivity was high for the detection of both classic and occult CNV activity (90.9% and 100% respectively) (one study).[29] Sensitivity of TD-OCT for detection of cystoid macular oedema and pigment epithelial detachment was low (22.9% and 5.7% respectively) (one study).[51] In two studies sensitivity was higher for detection of nAMD activity based on intraretinal fluid (90.3% and 82.9% respectively) compared with subretinal fluid (71.0% and 47.1% respectively).[31,51]

7 ASSESSMENT OF COST-EFFECTIVENESS

The health economic component of this study explored the evidence in cost-effectiveness of using OCT for diagnosis and/or monitoring of individuals with neovascular age-related macular degeneration (nAMD). For this, a two-step approach was used, with (1) a systematic review of economic evaluations to retrieve any readily available evidence on cost-effectiveness, followed by (2) a de-novo decision analytic model to synthesise the available evidence on effectiveness, health care resources used and costs. Section 7.1 reports the systematic review of cost-effectiveness studies and section 7.2 focuses on the economic model exercise.

7.1 Systematic review of economic evaluations

The aim of this review was to retrieve evidence, from the perspective of the UK NHS, on the cost-effectiveness of the use of OCT in the diagnosis and/or monitoring of individuals with nAMD. This was attempted by systematically identifying and quality assessing all economic evaluations comparing strategies that included OCT for diagnosing and/or monitoring of individuals with nAMD.

7.1.1 Inclusion and exclusion criteria

Inclusion criteria required the studies to be full economic evaluations,[54] that is, to consider cost and effects for more than one strategy, in order to be included in the review. No restrictions were imposed in the way cost and/or effects were calculated. In addition, at least one of the compared strategies for diagnosis or monitoring of nAMD had to include OCT. Finally, the studies were required to be performed in adults with nAMD.

7.1.2 Search strategy

Studies that reported both costs and outcomes in diagnosing AMD using OCT were sought from a systematic review of the literature. No language restrictions or limitations to searches were imposed.

Databases searched were Medline (1996 – November Week 2 2012), Embase (1980 - Week 45 2012), Medline In-Process (14th November 2012), NHS EED (October 2012), HTA Database (October 2012), Health Management Information Consortium (1979 – September 2012), Research Papers in Economics (RePeC) (September 2012) and ARVO Meeting Abstracts from April, 2009. In addition, reference lists of all included studies were scanned to identify additional potentially relevant studies. Full details of the search strategies used are documented in Appendix 2.

7.1.3 Results

From the database searches 473 hits (titles & abstracts) were retrieved; from these 44 studies were selected for full-text assessment. No studies fulfilled the inclusion criteria as none of these were diagnosis or monitoring interventions for individuals with nAMD.

7.2 Economic evaluation modelling exercise

The aim of the economic model was to determine the relative efficiency of strategies for diagnosis and monitoring of individuals with nAMD. Care pathways were developed within the Project Management Group and the Project Advisory Group meetings. The groups initially considered all possible tests (see Background chapter) and several combinations of these. After subsequent discussions a number of these options were excluded. For instance, FFA only was originally considered as one of the (monthly) monitoring pathways. However, this option was deemed unfeasible (i.e. FFA is an invasive test) and consequently dropped. Three different strategies were finally selected for the nAMD diagnosis and monitoring stages, respectively, giving a total of 9 diagnosis-monitoring combinations:

Diagnosis strategies

a) (Stereoscopic) fundus fluorescein angiography (FFA) interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge.
b) Optical coherence tomography (OCT) alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge.
c) Visual acuity (VA) and OCT and slit-lamp biomicroscopy (SLB) in all. If positive or unclear, then arrange for stereoscopic FFA. If negative, discharge. This is the strategy for diagnosis that best reflects standard practice.

Monitoring strategies

a) OCT alone (interpreted by an ophthalmologist). If positive, treat. If negative or unclear review in one month's time.
b) VA and SLB and OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in one month's time. If unclear, then the ophthalmologist will arrange for a stereoscopic FFA. This is the monitoring strategy that best reflects standard practice.
c) VA and OCT interpreted by a technician or nurse. If negative, review in one month's time. If positive or unclear, refer for ophthalmologist assessment (e.g. SLB and ophthalmologist's own interpretation of VA and OCT test results). The ophthalmologist will make a decision: if positive, treat; if negative, review in one month's time; if unclear, arrange for stereoscopic FFA.

Monitoring strategy d) has been included in the monitoring stage in order to explore the cost-effectiveness of the option, for example, of virtual clinics involving other healthcare professionals (e.g. nurses, technicians, etc). Virtual clinics are increasingly used in NHS services for monitoring patients with nAMD.[55]

Table 19 shows the final nine combined strategies incorporated into the decision model. All strategies considered monitoring on a monthly basis with a decision to treat when the disease was deemed active (i.e. retinal fluid on OCT). All monitoring strategies that relied on stereoscopic FFA as a final assessment step (e.g. monitoring strategies b and c) would treat if FFA positive, or review in a month's time if FFA negative. Treatment consisted of one injection only (i.e. 0.5mg ranibizumab) with review in one month's time.

Table 19 Strategies for the economic evaluation model

Strategy	Strategy Label	Diagnostic pathway	Monitoring pathway	Treatment
1	FFA & OCT	FFA interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	OCT alone (interpreted by an ophthalmologist). If positive, treat. If negative or unclear review in 1 month	1 monthly injection if disease deemed active
2	FFA & Ophthalmologist	FFA interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	VA and SLB and OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in a month's time. If unclear, then the ophthalmologist will arrange for stereoscopic FFA	1 monthly injection if disease deemed active
3	FFA & Nurse	FFA interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	VA and OCT interpreted by a technician or nurse. If negative, review in a month. If positive or unclear, referral for an ophthalmologist assessment (e.g. SLB and own interpretation of VA and OCT test results). If assessment positive, treat; if negative, review in a month time; if unclear, arrange for stereoscopic FFA	1 monthly injection if disease deemed active
4	OCT & OCT	OCT alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	OCT alone (interpreted by an ophthalmologists). If positive, treat. If negative or unclear review in 1 month	1 monthly injection if disease deemed active
5	OCT & Ophthalmologist	OCT alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	VA and SLB and OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in a month's time. If unclear, then the ophthalmologist will arrange for stereoscopic FFA	1 monthly injection if disease deemed active

Strategy	Strategy Label	Diagnostic pathway	Monitoring pathway	Treatment
6	OCT & Nurse	OCT alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	VA and OCT interpreted by a technician or nurse. If negative, review in a month. If positive or unclear, referral for an ophthalmologist assessment (e.g. SLB and own interpretation of VA and OCT test results). If assessment positive, treat; if negative, review in a month time; if unclear, arrange for stereoscopic FFA	1 monthly injection if disease deemed active
7	Ophthalmologist & OCT	VA, OCT and SLB in all interpreted by an ophthalmologist. If negative, discharge. If positive or unclear, then arrange for stereoscopic FFA. If FFA positive, treat and monitor; if negative, discharge	OCT alone (interpreted by an ophthalmologist). If positive, treat. If negative or unclear review in 1 month	1 monthly injection if disease deemed active
8	Ophthalmologist & Ophthalmologist	VA, OCT and SLB in all interpreted by an ophthalmologist. If negative, discharge. If positive or unclear, then arrange for stereoscopic FFA. If FFA positive, treat and monitor; if negative, discharge	VA and SLB and OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in a month time. If unclear, then the ophthalmologist will arrange for stereoscopic FFA	1 monthly injection if disease deemed active
9	Ophthalmologist & Nurse	VA, OCT and SLB in all interpreted by an ophthalmologist. If negative, discharge. If positive or unclear, then arrange for stereoscopic FFA. If FFA positive, treat and monitor; if negative, discharge	VA and OCT interpreted by a technician or nurse. If negative, review in a month. If positive or unclear, referral for an ophthalmologist assessment (e.g. SLB and own interpretation of VA and OCT test results). If assessment positive, treat; if negative, review in 1 month; if unclear, arrange for stereoscopic FFA	1 monthly injection if disease deemed active

Note: FFA (stereoscopic fundus fluorescein angiography); OCT (optical coherence tomography); VA (visual acuity); SLB (slit-lamp biomicroscopy).

7.2.1 The economic model

A Markov model approach was selected for the decision analytic model exercise.[56-59] Markov models have Markov states where individuals spend a period of time, named a 'cycle'. At the end of each cycle the individuals can remain in their current Markov state or move to another state. The probabilities of moving to other Markov states or remaining in the current state are named 'transition probabilities'. Individuals in the model would accrue costs and benefits (e.g. 'life years') depending on the time spent in each Markov state and the interventions and/or events modelled within each Markov state. Markov models are particularly suitable to model recurrent issues and chronic diseases. They allow incorporating health states to reflect the movement of the patients during diagnosis-monitoring. In the current study, model states reflect the underlying condition (e.g. nAMD active or inactive) together with the decision on treatment (e.g. treated or untreated nAMD) and visual acuity states of the individuals (Table 20). In all these models, an absorbing state is included where all individuals would end up if the model was run for a sufficiently long period of time (e.g. death state).

The present model incorporates a first diagnosis stage combined with a recurrent (monthly) monitoring phase.

The Markov models

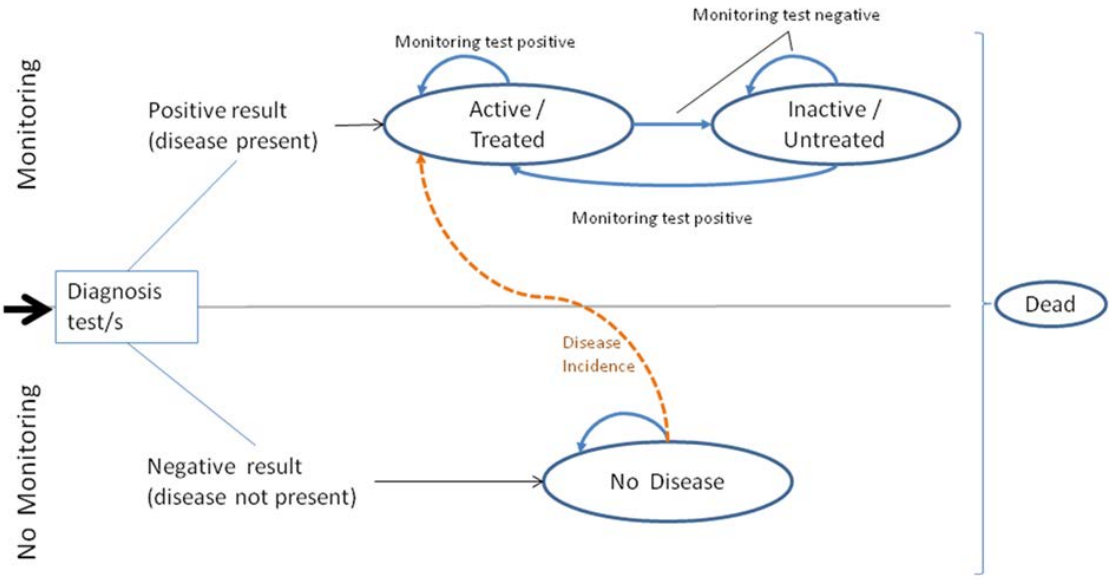
This section presents a stepwise introduction to the Markov models used to compare the alternative strategies. Individuals' visual acuity status is set aside for the moment to focus on the other two issues and assumptions underpinning the movement of individuals throughout the model: (1) the underlying disease condition (e.g. if the disease is present or not and, if present, its active or inactive status) as well as (2) the diagnosis or monitoring test results on which the treatment decision will depend (i.e. a positive result will trigger a decision to treat and a negative results will trigger a decision not to treat). Figure 13 shows the schematic diagram of the final model used for the economic evaluation for this study.

This section presents three schematic diagrams for this model. The figures differ in the assumptions made with respect to the information retrieved from the diagnosis and/or monitoring test or assessments. Namely, if perfect information from the tests or assessments is assumed, then there would be no false positive or false negative results (i.e. equivalent to assuming sensitivity and specificity are equal to 1). That is, the underlying condition is detected with certainty. When this assumption is relaxed, then the possibility of incorrect assessments appears.

Perfect information from diagnosis and monitoring tests

Figure 11 assumes perfect information at diagnosis and monitoring stages in the model. The whole modelled cohort starts at the black arrow on the left hand side of the figure (corresponding to an initial Markov model stage). The assumption of perfect information means that, at diagnosis stage, all individuals with the disease will have a positive result while all those without the disease will obtain a negative result. Individuals with a positive result will go to a monitoring scheme while those with a negative result will be discharged. Those individuals with the disease and positive results will start within a Markov model state with an "Active disease and under Treatment" (e.g. 'Active/Treated' state). Note that 'Active' refers to the underlying condition while 'Treated' or not depends on the test or assessment result.

Figure 11 Markov model schematic diagram assuming perfect information at diagnosis and monitoring stages



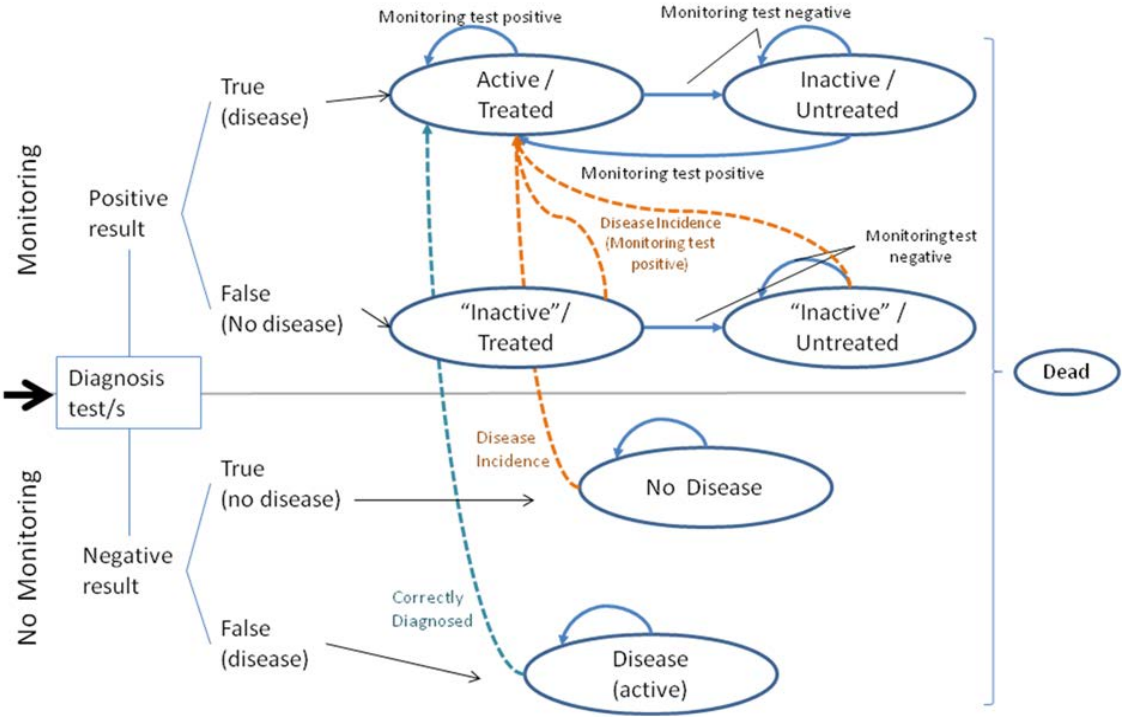
Assuming monthly monitoring visits and assessments, a positive result at a monitoring visit means the individual's disease is active (assuming, again, perfect information and no possibility of false positive or false negative results) and will therefore mean that the person remains in the 'Active/Treated' Markov state. If a negative result from the monitoring assessment is obtained, then it would mean that the individual's disease has become inactive and the decision not to administer treatment will follow. In this case, the individual will move to the 'Inactive/Untreated' Markov state. At each Markov cycle (monthly) individuals can become active or inactive; this status would be detected at the next monitoring visit with a positive or negative result, and the individual will either move or stay in the corresponding Markov model state with a consistent treatment decision.

Individuals without the disease at the moment of first diagnosis could develop the disease in the future (i.e. incident cases among the population). In the model (Figures 11 to 13), it was assumed that these individuals would be correctly diagnosed within a second visit and eventually moved to be monitored within the 'Active/Treated' state. Finally, the "Dead" state is the absorbing state in this model (i.e. a state that individuals cannot move out of); individuals can move from any other Markov state into the 'Dead' absorbing state.

Imperfect information from diagnosis test combined with perfect information from monitoring tests

Figure 12 shows a similar schematic diagram but in this case there is imperfect information at the moment of first diagnosis. After this initial diagnostic intervention, further diagnosis and/or monitoring assessments will be done with certainty (e.g. assuming perfect information). This opens the possibility of obtaining true as well as false positive and negative results from the initial diagnosis test/s. Individuals with positive results, therefore, might not have nAMD while individuals with negative diagnostic test results might actually have the disease. This situation will have an effect on the Markov states the individuals will start at after diagnosis. Those with a true positive result will start with their active disease being treated and eventually move to an inactive state (e.g. 'Inactive/Untreated') depending on the treatment effect. Individuals with a false positive result will not have nAMD but will be treated and monitored. However, this treatment cannot be effective as these people did not have the disease. As this schematic diagram assumes perfect information at the monitoring phase, these individuals would be correctly assessed in their subsequent monitoring visits, moving to the '"Inactive"/Untreated' state.

Figure 12 Markov model schematic diagram assuming imperfect information at diagnosis and perfect information at monitoring stage



Note: "Inactive"= underlying condition regarded as inactive nAMD when the disease was actually not present.

In addition, if the person has a negative result at diagnosis, this could be a true negative or a false negative result. In either case the individual would be discharged under the belief that nAMD was not present. If true negative, meaning that the disease was not present, the individual will start at the 'No Disease' state and will remain at that stage unless they develop nAMD. If false negative (patients with the disease and negative test) the person will start within the 'Disease (active)' state.

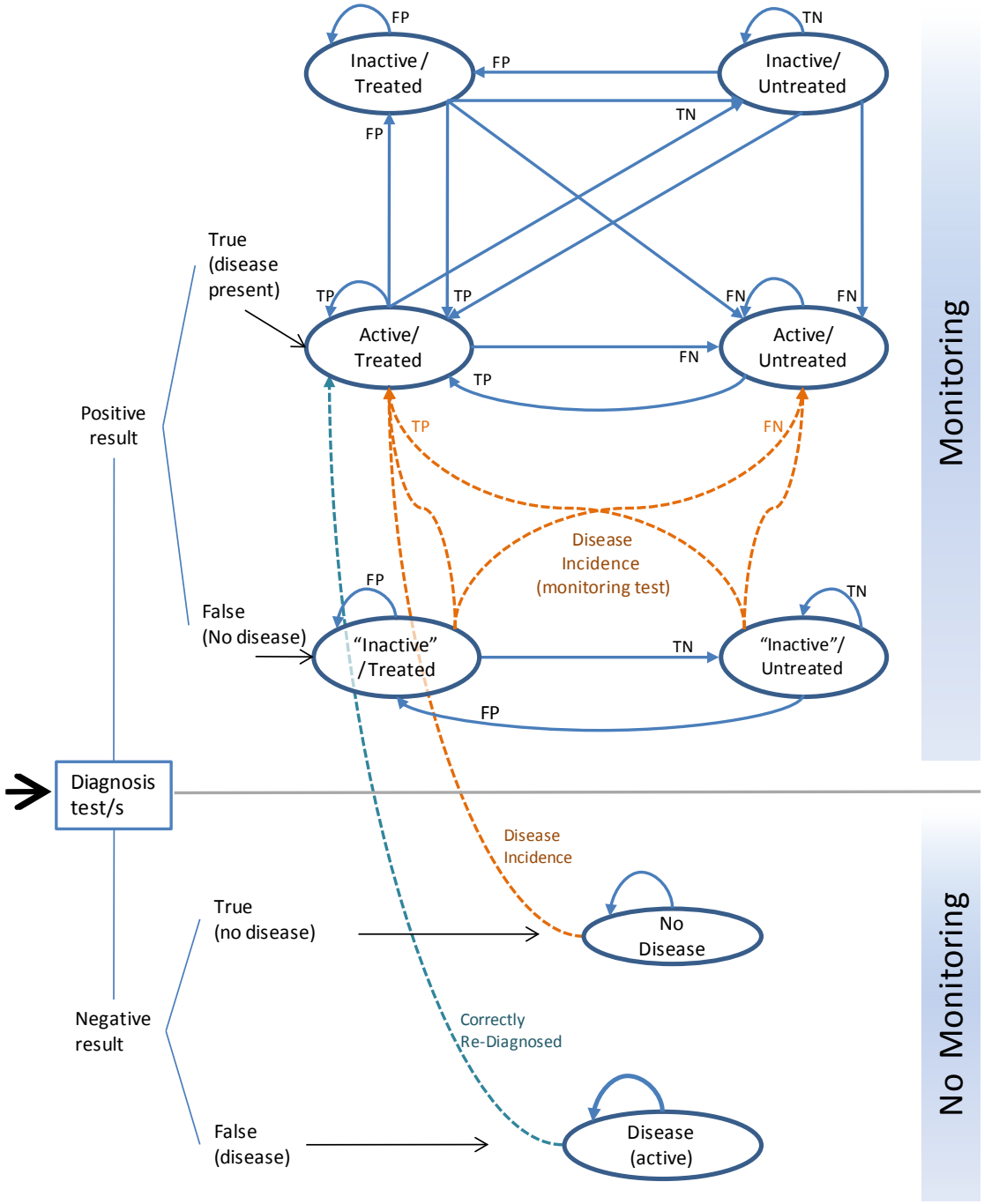
Finally, an identical assumption of using FFA for diagnosis for those presenting for a second time (re-diagnosis) is followed for those with false negative results at first diagnosis. These people will start to be monitored and moved to the 'Active/Treated' state after second presentation for diagnosis. A further assumption is used for this sub-group: based on expert opinion, these nAMD individuals that have been missed at first diagnosis will present for re-diagnosis within three months. The rationale behind this was the natural history of the disease and the belief that nAMD would advance with visual acuity deterioration making the individual return for a further eye check.

Imperfect information from diagnosis and monitoring tests

Figure 13 shows the schematic diagram for the actual Markov model used. In this case, imperfect information at diagnosis as well as monitoring phases was assumed. The cases for those with first diagnosis negative results are identical to those in Figure 12 (lower part of Figure 13). However, the diagram for those with positive results at first diagnosis will differ.

Individuals with true positive results at first diagnosis will start as before within the 'Active/Treated' state. After this, depending on the underlying condition (e.g. active or inactive) and the monitoring assessment result (e.g. positive or negative, with a positive result reflecting the presence of disease activity), individuals will move to alternative Markov states (e.g. 'Inactive/Untreated'; 'Inactive/Treated'; 'Active/Untreated'). The arrows in the figure show the direction in which individuals can move due to their underlying condition and assessment while the arrow labels refer to the result of the assessment (e.g. TN: true negative, TP: true positive, FN: false negative, FP: false positive).

Figure 13 Markov model schematic diagram assuming imperfect information at diagnosis and monitoring stages



Note: TN = True Negative result; TP = True Positive result; FN = False Negative result; FP = False Positive result; "Inactive" = means apparent inactivity but actually no disease was ever present.

A further assumption in the model is that those individuals under monitoring who do not have nAMD (i.e. "Inactive" states) that subsequently become nAMD would be detected by the monitoring strategy test/s. This monitoring strategy could include FFA (perfect information test) or other non-perfect information test (e.g. OCT alone). Therefore, these individuals that now have nAMD could move to 'Active/Treated' or 'Active/Untreated' depending on positive or negative monitoring assessment, respectively.

7.2.2 Markov model states and health status valuation link

The former diagrams show how individuals can move in the model according to their underlying condition and the result of the test/s or assessments. However, it is not possible to attach utility weights to these Markov states. In essence, individuals can experience alternative active or inactive disease but no difference in their reported health status. The economic model attaches utility weights according to, mainly, visual acuity. Therefore, the effect on health status will come through the deterioration in visual acuity, while visual acuity deterioration will result from the fact of individuals being misdiagnosed (e.g. no nAMD when actually the disease was present) or misclassified as inactive when their true condition was active nAMD.

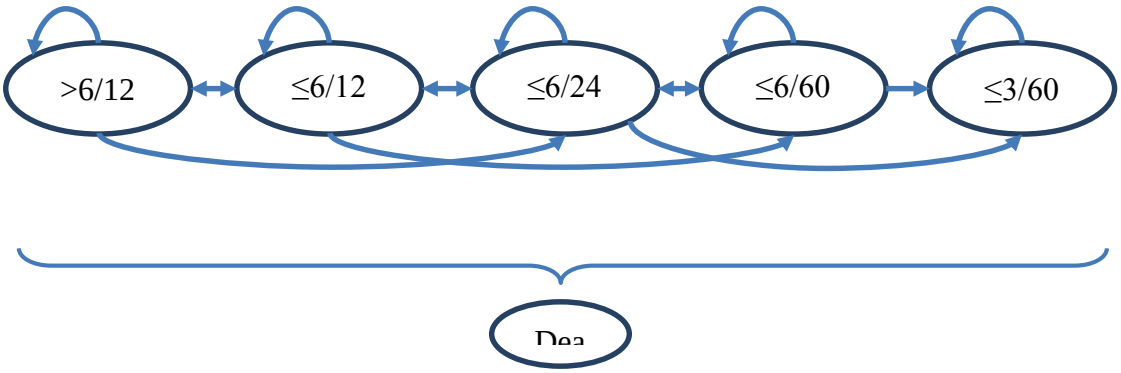
In terms of the presented diagrams, the number of Markov states is multiplied by the number of visual acuity ranges considered by the model. Therefore, there is a trade-off between the number of visual acuity ranges in order to reflect differences in visual acuity - and patient reported health status - and the model complexity. Utility differences between the alternative model strategies result from the different periods of time individuals are misclassified within each strategy. It was considered that five visual acuity states (Table 20) would give sufficient refinement for utility differences to be reflected. This approach has been used in other models in this area of healthcare.[60] Therefore, each strategy (i.e. each Markov model) has 32 Markov model states (e.g. four visual acuity states times six monitoring states, plus four visual acuity states times one nAMD undiagnosed state, plus profound visual loss/blindness, a 'No disease' state –normal visual acuity only–, the absorbing state 'Dead', and an initial state for first diagnosis).

Table 20 Visual acuity states

	Visual health states (Snellen fractions)	Visual health status
1	>6/12	Normal visual acuity
2	≤6/12 to > 6/24	Mild visual acuity loss
3	≤6/24 to > 6/60	Moderate visual acuity loss
4	≤6/60 to > 3/60	Severe visual acuity loss
5	≤3/60	Profound visual loss/blindness

Figure 14 shows a Markov model schematic diagram for the visual acuity states considered in the model. Arrows in the figure show the possible movements in the model in one cycle (e.g. one month). Individuals' visual acuity can remain the same, improve or deteriorate in one particular cycle. Individuals can have their visual acuity improved and move one level up at the end of a cycle; however, their visual acuity can deteriorate and move one or two levels down from their current visual acuity state. Finally, the model considered that a visual acuity deterioration of ≤3/60 (i.e. profound visual loss/ blindness) was not reversible and the individual was referred to supportive care.

Figure 14 Markov model schematic diagram for visual acuity states



Parameter estimates used in the economic model

The parameter estimates required to populate the economic model were obtained from the systematic review of diagnostic and monitoring studies (see chapter 6) as well as structured and focused literature searches. When no suitable data resulted from these searches, expert opinion was sought. The next section gives details of the probabilities, unit costs and utility weights used in the model. The section also provides details of the probability distributions used for the probabilistic sensitivity analysis.[61] Probabilistic sensitivity analysis involves attaching probability distributions to model parameters and conducting a number of Monte Carlo

simulations (e.g. 1000). In each of these simulations a set of parameter values will be drawn from the attached distributions, the model is run and results calculated. It is possible then to obtain a distribution of the model cost-effectiveness results that reflects the overall parameter uncertainty in the economic evaluation model.[62,63]

7.2.3 Probabilities

Table 21 shows data on nAMD prevalence, incidence and visual acuity at the start of the model run. Recently, Colquitt et al.[60] reviewed studies assessing the prevalence and incidence of AMD and nAMD. The setting for this economic evaluation was secondary care; therefore the prevalence rate to inform the model should be that corresponding to the group of individuals referred to Hospital Eye services with a suspected nAMD diagnosis. The prevalence rate used was obtained from the literature retrieved by the systematic review of test accuracy and agreed within the project management and advisory groups. An overall incidence of 1% per year was used based on Mitchell et al.[64] Incidence figures presented by Mitchell et al. for Australia were similar to the results by Van Leeuwen et al. for the Rotterdam study but were reported in a form that could be readily incorporated into the economic model.[65] Mortality data were obtained from Interim Life Tables for England and Wales (2009-2011). No difference in mortality rates were found when comparing age specific mortality rates form the Interim Life Tables and those from the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT)[8] and the Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN)[9] studies. Therefore, no excess mortality was included due to nAMD.[66,67] However, excess mortality risk was incorporated for the last disease visual acuity stage (profound visual loss/blindness – visual acuity $\leq 3/60$).

Table 21 also shows probability distributions defined for the probabilistic sensitivity analysis. Uninformative uniform distributions were used for nAMD prevalence and profound visual loss/blindness excess mortality. Ranges for defining these were assumptions based on data from the literature if available (e.g. from the review of test accuracy). A gamma distribution was defined for nAMD incidence based on mean and standard deviation (e.g. 1/10 of the mean) using the tool provided by Treeage (TreeAge Software, Inc., Williamstown, MA, 2013).

Table 21 Prevalence, incidence, and visual acuity at start

Variable	Value	Probability Distribution	Source
Epidemiological data			
Prevalence for nAMD	70%	Uniform(0.6; 0.8)	Expert opinion and articles from SR test accuracy
Incidence rate of nAMD (monthly)	0.084%	Gamma(1; 1190)	Mitchell et al[64]
Mortality	various		Interim Life Tables, England & Wales (2009-2011)[14]
Profound visual loss/blindness excess mortality	17%	Uniform(0.1; 0.5)	Assumption
Cohort details at Start			
Age (years)	65	n/a	Assumption based on expert opinion
Mean Visual Acuity			
Individuals with nAMD:			
≤6/12 to > 6/24 state	100%	n/a	Assumption based on expert opinion and CATT and IVAN RCTs mean VA at start
Individuals without nAMD:			
>6/12	100%	n/a	Assumption based on expert opinion

The cohort start age was set at 65 years as this is the age where particular changes are observed in the retina and macula (personal communication – Dr. Noemi Lois and Project Advisory Group). In addition, mean visual acuity at start was set at between ≤ 6/12 to > 6/24 for those individuals with nAMD. This was agreed to be the most common visual acuity at presentation by experts and also the mean visual acuity at baseline in the CATT and IVAN studies.[8,9]

Table 22 presents diagnostic test performance data. As mentioned above, three strategies were defined for diagnosis within the economic model. For each of these strategies, sensitivity and specificity data were needed, specifically for FFA, OCT, and Ophthalmologist assessment (i.e. with visual acuity test, SLB, and the results from the OCT). FFA interpreted by an ophthalmologist was stated as the reference standard for the diagnosis of nAMD; therefore, perfect information was assumed from this test, with sensitivity and specificity equal to 1. OCT sensitivity and specificity were obtained from the systematic review of diagnostic studies. These data correspond to OCT pooled estimates (four studies, number of eyes 406.[26,39,45,48] No studies were identified on the ophthalmologist assessment diagnostic performance. Hence, sensitivity and specificity estimates were derived from expert opinion.

Table 22 Test performance parameters - diagnosis of nAMD

Variable	Value	Range	Probability Distribution	Source
FFA				
Sensitivity	1	n/a	n/a	Assumption
Specificity	1	n/a	n/a	Assumption
OCT				
Sensitivity	0.88	(0.46, 0.98)	Beta(36.3; 4.9)	Systematic review of diagnostic studies
Specificity	0.78	(0.64, 0.88)	Beta(82.9; 23.4)	Systematic review of diagnostic studies
Ophthalmologist assessment (with VA, OCT and SLB)				
Sensitivity	0.99		Beta(0.22; 0.002)	Assumption based on expert opinion, using the systematic review results as a starting point
Specificity	0.9		Beta(9.1; 1)	Assumption based on expert opinion, using the systematic review results as a starting point
Unclear	0.1	(0 to 0.5)	Beta(89.9; 809.1)	Assumption based on expert opinion

Sensitivity and specificity data are bounded between zero and 1. Therefore, beta distributions were defined for probabilistic sensitivity analysis. For OCT, these were obtained using mean values and standard deviation in order to obtain values within the 95% CI provided by the systematic review of diagnostic studies (see chapter 6, Table 17). Probability distributions for ophthalmologist diagnosis assessment were obtained using the approximation tool provided by Treeage based on mean and standard deviation (e.g. 1/10 of mean).

Table 23 shows similar data to Table 22 but for monitoring of individuals with nAMD. FFA was also stated as the reference standard to detect disease activity; therefore, perfect information was assumed, with sensitivity and specificity defined as equal to 1. OCT monitoring sensitivity and specificity data were obtained from the systematic review of test performance (chapter 6). Pooled estimates, (e.g. four studies, N=242), were used.[15,27,29,52] No studies were identified reporting the diagnostic performance of nurse or technician assessment, or for ophthalmologist assessment. Therefore, estimates for the sensitivity and specificity of these strategies were derived from expert opinion.

Table 23 Test performance data - monitoring of nAMD

Variable	Value	Range	Probability Distribution	Source
FFA				
Sensitivity	1	n/a	n/a	Assumption
Specificity	1	n/a	n/a	Assumption
OCT				
Sensitivity	0.85	(0.72, 0.93)	Beta(105; 18.5)	Systematic review of monitoring studies
Specificity	0.48	(0.30, 0.67)	Beta(32.8; 35.5)	Systematic review of monitoring studies
Technician/nurse assessment (VA and OCT)				
Sensitivity	0.9		Beta(108.9; 12.1)	Assumption based on expert opinion, using the systematic review results as a starting point

Variable	Value	Range	Probability Distribution	Source
Specificity	0.6		Beta(72.6; 48.4)	Assumption based on expert opinion, using the systematic review results as a starting point
Unclear	0.1		Beta(89.9; 809.1)	Assumption based on expert opinion
Ophthalmologist assessment (VA, OCT & SLB)				
Sensitivity	0.97		Beta(2.51; 0.08)	Assumption based on expert opinion, using the systematic review results as a starting point
Specificity	0.8		Beta(19.2; 4.8)	Assumption based on expert opinion, using the systematic review results as a starting point
Unclear	0.1		Beta(89.9; 809.1)	Assumption based on expert opinion

A similar approach to the one used for the sensitivity and specificity of diagnostic tests was used for this information for monitoring tests. Beta probability distributions were approximated and defined using mean and standard deviation (e.g. 1/10 of the mean) values. The range of values of OCT used in the model did not exceed the 95% CI values obtained from the systematic review of monitoring studies (i.e. OCT range data in Table 23).

Disease progression in the model was defined in terms of visual acuity changes. Gaining or losing three lines in the Snellen chart (approximately 15 letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) chart) was assumed to make individuals move from their current Markov model state to the next level (see Table 20 and Figure 14). Data for this were obtained

from Rosenfeld et al. (i.e. MARINA study).[68] This study was based in the USA, involved 716 participants and compared monthly treatment with ranibizumab (0.3mg, N = 238 or 0.5mg, N=240) against sham injection (N = 238). Data from treatment (0.5 mg) and control groups were used to calculate monthly progression probabilities for active treated and non-treated individuals, respectively. No visual acuity progression was assumed for nAMD inactive individuals as well as non-AMD individuals.

Table 24 Disease progression data – visual acuity

	Year 1		Year 2 onwards	
	Value	**Probability distribution**	**Value**	**Probability distribution**
Treatment				
Gain at least 3 lines	0.0338	Beta(96.6; 2761.9)	0.0167	Beta(98.3; 5777)
Gain or lose less than 3 lines	Default		Default	
Lose between 3 and 6 lines	0.0036	Beta(99.6; 27817)	0.0032	Beta(99.7; 30634)
Lose 6 lines or more	0.0010	Beta(99.9; 99252)	0.0011	Beta(99.9; 94640)
No treatment				
Gain at least 3 lines	0.0043	Beta(99.6; 23244)	0.0016	Beta(99.8; 61799)
Gain or lose less than 3 lines	Default		Default	
Lose between 3 and 6 lines	0.0221	Beta(97.8; 4331)	0.0116	Beta(98.8; 8431)
Lose 6 lines or more	0.0128	Beta(98.7; 7627)	0.0107	Beta(98.9; 9171)

Beta distributions were attached to visual acuity progression data for probabilistic sensitivity analysis (Table 24). Unfortunately there were no data available to construct confidence intervals around mean values used in the model. As such, probability distributions parameter values were developed using mean values and assuming 1/10 of mean values for standard errors.

Additional data were required on disease status, namely, the probability of becoming active when the individual's disease was inactive and under no treatment, as well as the probability of becoming inactive when the individual's disease was active and under treatment. First year data

for these were developed using data from the IVAN study (personal communication – Dr. Chris Rogers, 12th June 2013). The IVAN study was a 2x2 factorial design and adult individuals with untreated nAMD were randomised into four groups: ranibizumab or bevacizumab, given either every month (continuous) or as needed (discontinuous). All individuals were reviewed on a monthly basis. Survival data for participants' first treatment failure (e.g. subretinal fluid, increasing intraretinal fluid, or fresh blood) for the discontinuous arm (N=302) were used to develop mean probability values. All individuals were active at baseline and 95% of these did not fail the retreatment criteria (e.g. did not need to be treated) at 3 months. This rate was used to obtain the monthly probability of becoming inactive when active and under treatment.[61] At month six, 54% of individuals were still inactive. The difference between the proportion of inactive individuals at months three and six was used to develop the probability of becoming active when inactive and under no treatment (Table 25). Probability distributions were developed using the 95% CI from the IVAN study survivor function using Crystal Ball software (Table 25).

Table 25 Disease progression data - active and inactive nAMD

Variable	Value	Probability Distribution	Source
Probability of becoming:			
Inactive when active and under treatment			
Year 1	0.616	Beta(176.6; 110)	based on data from IVAN study[9]
Year 2 onwards	0.365	Beta(63.1; 110)	based on data from CATT study[8]
Active when inactive and under no treatment			
Year 1	0.306	Beta(148; 335)	based on data from IVAN study[9]
Year 2 onwards	0.097	Gamma(100; 1029)	based on Hörster et al[69]
Active when inactive and under treatment	0.5 x Active when inactive and under no treatment		

Second year data for the probability of becoming inactive were developed using data from the CATT study. The inclusion criteria and the treatment group for the CATT study were similar to that of the IVAN study. However, within the IVAN study three monthly injections were administered when participants failed the disease inactive criteria. The CATT study administered one injection only and reviewed participants in one month's time before making a further treatment decision. A monthly probability was sought in order to obtain the CATT study mean number of injections within the as needed arm at two years. A beta distribution was attached based on mean value and 1/10 of the mean value as standard error (Treeage software).

Second year data for the probability of becoming active when participants were inactive and under no treatment was developed using data reported by Hörster et al.[69] The authors reviewed data on all patients receiving intravitreal ranibizumab injections for nAMD at the University of Cologne. Eyes with at least two recurrences (i.e. re-appearance of intraretinal or subretinal fluid on OCT, and/or leakage on angiography) were selected. The mean follow-up time (months) and number of recurrences were 28.8 and 2.8 respectively.

A number of individuals that were inactive at three months within the monthly treatment group in the IVAN study[9] failed the no re-treatment criteria (e.g. subretinal fluid, increasing intraretinal fluid, or fresh blood) in subsequent months. This means that, even under monthly treatment, inactive individuals could become active again. Based on this, half the probability of becoming active when inactive and under no treatment was assumed for the probability of becoming active when inactive and under treatment.

Diagnosis or monitoring strategies could result in over- or under-treatment; therefore, it was believed important to include adverse events as a result of treatment. Two recent studies[8,9] report systemic and ocular adverse event rates. It was not clear from inspection of these data that systemic adverse events could be due to treatment of nAMD. Therefore, only ocular adverse events were included in the model. Table 26 shows monthly estimates for the proportion of individuals that were under treatment that experienced cataract, endophthalmitis, glaucoma, retinal detachment and uveitis.

Table 26 Adverse events

Variable	Value (monthly %)	Source
Cataract	0.34%	The CATT Research Group[8]
Endophthalmitis	0.40%	The CATT Research Group[8]
Glaucoma	0.05%	The CATT Research Group[8]
Retinal detachment	0.03%	The CATT Research Group[8]
Uveitis	0.03%	The CATT Research Group[8]

7.2.4 Costs

Table 27 shows cost estimates used in the model. Prices are expressed in 2011-2012 pounds sterling (£). Strategy assessment costs were a combination of the cost of a visit (e.g. ophthalmologist, nurse or technician) and the cost of a particular test used for the assessment (e.g. FFA or OCT). For instance, the diagnosis cost for strategies where diagnosis was conducted using FFA only was calculated adding up the cost of an ophthalmologist visit and the cost for an FFA (e.g. £79.74 + £117.26 = £197.00). NHS Reference Costs were used for all but the ranibizumab unit costs in Table 27, for which BNF data were used (£742.17).[70] The unit cost for face-to-face consultant-led follow-up attendance that resulted in non-admission for the Ophthalmology service was used for the cost of a diagnosis or monitoring visit to the ophthalmologist (£79.74). Likewise, non-consultant led was used for the cost of a nurse or technician monitoring visit (£58.53). Minor Vitreous Retinal Procedures cost category (HRG BZ23Z code) was used to cost FFA (£117.26). Finally, after consultation with clinical experts, an ultrasound scan (HRG RA23Z Ultrasound Scan, less than 20 minutes) was deemed more likely to reflect the cost of an OCT test (£51.27).

Table 27 Unit costs

Variable	£ (2011-2012)	Range	Probability Distribution	Source
Ophthalmologist visit	79.74	(68; 86)	Gamma (309.9; 3.9)	NHS Reference Costs (Consultant Led: Follow-up Attendance Non-Admitted Face-to-face. 130: Ophthalmology)
Nurse / Technician visit	58.53	(42;71)	Gamma (34.3; 0.59)	NHS Reference Costs (Non-Consultant Led: Follow-up Attendance Non-Admitted Face-to-face. 130: Ophthalmology)[70]
Fundus fluorescein angiography	117.26		Gamma (25; 0.21)	NHS Reference Costs (HRG BZ23Z Minor Vitreous Retinal Procedures)[70]
Optical coherence tomography	51.27	(32;62)	Gamma (48.8; 0.95)	NHS Reference Costs 2011-12. (HRG RA23Z Ultrasound Scan, less than 20 minutes)[70]
Treatment				
Medication ranibizumab (Lucentis®)	742.17		Gamma (4; 0.01)	BNF[71]

Gamma probability distributions were defined for unit cost data for probabilistic sensitivity analysis as these are defined non negative and provide a possibility of a right tail that could account for few very high unit cost cases. Ranges for Reference cost based data are also reported in Table 27; these are Lower and upper quartiles. These were used to tailor cost probability distributions.

The cost of profound visual loss/blindness from the NHS and Personal Social Services perspective was calculated following Colquitt et al.[60] The authors used proportion for service utilisation developed by Meads et al. (Table 28).[72] The unit costs reported by Colquitt et al.[60] were updated using Hospital and Community Health Service (HCHS) specific price inflation index (base 2005=100) for March 2012 (e.g. £121.85). Using alternative weekly cost figure of £497 for residential care (the item in the list with higher unit cost) reported by Curtis,[73] results

in an annual cost of £556 and £537 for the first and subsequent years, respectively, and were used as the basis for deterministic sensitivity analysis.

Table 28 Cost of profound visual loss/blindness

	Requiring (%)	Cost (£, 2005)	Cost (£, 2012)	Annual Cost (£)	Monthly Cost (£)
Severe sight impairment registration	95%	115	140	£133	£11.09
Low-vision aids	33%	150	183	£60	£5.03
Low-vision rehabilitation	11%	259	316	£35	£2.89
Community care	6%	6,552	7,984	£479	£39.92
Residential care	30%	13,577	16,544	£4,963	£413.59
Depression	39%	431	525	£205	£17.07
Hip replacement	5%	5,379	6,554	£328	£27.31
Total year 1				£6,203	£517
Total year 2+				£5,975	£498

7.2.5 Utility weights

Guidelines for economic evaluation of health care technologies in the UK advocate the use of a preference-based measure of utility.[74] We conducted a focused search for these data for AMD individuals. It was confirmed that one group had the majority of studies in this area[75,76] and data from Brown et al.[75] were included in the economic model. The study by Brown et al. used the time trade-off approach on 72 consecutive patients seen at the Retina Vascular Unit at Wills Eye Hospital, Philadelphia, USA, to obtain utility weights for alternative visual acuity scores[76]. Table 29 presents utility weights used in the economic model according to the Markov model health state. Confidence intervals were also obtained from Brown et al.[75] Mean utility weights and confidence intervals were used to define beta distributions (Table 29) for probabilistic sensitivity analysis.

Table 29 Utility weights

Health State	Mean	95% CI	Probability Distribution	Source
>6/12	0.89	(0.82 to 0.96)	Beta(12.7; 1.6)	Colquitt et al[60] based on Brown et al[75]
≤ 6/12 to > 6/24 state	0.81	(0.73 to 0.89)	Beta(18.7; 4.4)	
≤ 6/24 to > 6/60 state	0.57	0.47 to 0.67)	Beta(42.4; 32)	
≤ 6/60 to > 3/60 state	0.52	(0.38 to 0.66)	Beta(51.4; 47.4)	
≤ 3/60	0.4	(0.29 to 0.50)	Beta(59.6; 89.4)	
Utility decrements (monthly) due to adverse events				Brown et al [76]
Cataract	0.012			
Endophthalmitis	0.025			
Retinal detachment	0.023			
Uveitis	0.025			assumed equal to Endophthalmitis

Utility decrements due to adverse events were retrieved from Brown et al.[76] The authors derived utility values from 233 patients with AMD and decrement values were obtained from individuals who experienced alternative adverse events. Table 29 shows the (monthly) utility decrements used within the model. These were applied to the proportion of individuals who experienced an adverse event from within those that were under treatment (Table 26). Searches were conducted to retrieve information on the effect of treatment injections on the quality of life of patients with nAMD; however no evidence was found. Moreover, from discussions within the Project Advisory Group and clinical experts, anxiety seemed to be associated with the uncertainty of the disease condition (i.e. active or inactive) rather than the treatment itself. Adding a utility decrement for each monthly monitoring visit for all strategies would have had no effect on the final results. As such, no utility adjustments were conducted due to treatment injections.

7.2.6 Base case and sensitivity analyses

The UK NICE guidelines of methods for technology appraisals were followed.[74] The model base case analysis was run for a cohort of 65 year old men for a time horizon of 35 years

(lifetime). A one month cycle length was defined. The analysis was conducted from the NHS and Personal Social Services perspective. Costs were expressed in 2011-2012 pounds sterling and effectiveness in quality-adjusted life years (QALYs). Costs and QALYs were discounted at 3.5%.[74] Cost-effectiveness analysis results are reported using incremental cost-effectiveness ratios (ICERs).[54] ICERs are calculated as the ratio between the difference in average cost between two alternative strategies and the difference in average QALYs. This ratio measures the additional cost that would have to be paid in order to obtain an extra unit of effectiveness (i.e. an extra QALY). Probabilistic analysis results are reported using cost-effectiveness acceptability curves (CEACs).[77,78] CEACs show the probability of a particular strategy to be cost-effective at alternative values of willingness to pay for an extra QALY.

Sensitivity analysis

Uncertainty in the economic model was explored conducting one-way sensitivity analysis, scenario analysis and probabilistic sensitivity analysis. As mentioned above, the base case analysis was run for a male cohort. Gender specific data were not available and the only different data for men and women were mortality rates. Female mortality data show longer life expectancy. These could result in longer time for benefits, but also costs. A further analysis was conducted using mortality data for women to observe the effect of longer life expectancy in the model results.

One-way sensitivity analyses were conducted on test diagnosis sensitivity and specificity, the probability of ophthalmologist diagnosis or monitoring results being unclear, tests and assessment monitoring sensitivity and specificity, probability of the nurse or technician assessment being unclear, and unit costs for OCT, FFA and ranibizumab.

Further deterministic sensitivity analyses were conducted using alternative discount rates for costs and QALYs, as well as prevalence rates for nAMD. In addition, population utility weights were retrieved from Czoski-Murray et al.[79] The authors elicited time trade-off based utility values from 108 healthy individuals for AMD states simulated using contact lenses.

Given base case and sensitivity analyses results, three scenario analyses were tested. All of these incorporated data that favoured OCT (Table 30). Scenario 1 used the upper limit for the 95% CI for OCT sensitivity and specificity for diagnosis and monitoring obtained from the systematic review of diagnostic and monitoring studies, together with £20.90 and £139 unit costs for OCT and FFA, respectively. Scenario 2 used the same data as for scenario 1 but assuming a cost per treatment injection of £50 instead of £742. Finally, scenario 3 assumed the same input data as for scenario 1 but monitoring pathways that based their decisions on OCT

only considered the unit cost of the OCT test for the monitoring visit as that of the OCT test for an optometry community service (£20.90).[80] The cost of an ophthalmologist visit was not considered in every monitoring visit but added only if the patient needed to be treated. This scenario explores the effect of monitoring patients within the community and only refers them to secondary care for treatment.

Table 30 Input data for scenario analyses

Variable	Diagnosis	Monitoring	Source
FFA			
Sensitivity	0.99	0.99	Assumption
Specificity	0.99	0.99	Assumption
OCT			
Sensitivity	0.98	0.93	Systematic review of diagnostic and monitoring studies
Specificity	0.88	0.67	Systematic review of diagnostic and monitoring studies
Unit costs	(2011-2012 £)		
FFA	139		NHS Reference Costs 2011-12. (HRG BZ23Z Minor Vitreous Retinal Procedures)[70]
OCT	20.9		General Ophthalmic Services: Increases to NHS Sight Test Fee.[81]

Base case and selected sensitivity analyses are presented in the next section. Full sensitivity analysis results are reported in Appendix 9.

7.2.7 Results

Table 31 reports base case analysis results for men for the nine compared strategies. Model strategies are ordered in terms of average cost in an ascending order. Diagnosis with FFA combined with the nurse or technician-led monitoring strategy (e.g. nurse or technician as first monitoring contact conducting a VA examination and interpreting OCT test results; if negative discharge, if positive or unclear, refer to an ophthalmologist for further assessment) was the

strategy with the lowest average total cost. The next non-dominated strategy (i.e. dominated strategy meaning a strategy with higher expected costs and lower expected QALYs) is diagnosis based on FFA only, followed by ophthalmologist-led monitoring. This strategy has higher total expected cost but also produces higher total expected QALYs. However, the incremental cost for an extra QALY (i.e. ICER) to adopt this strategy is above the often accepted cost-effectiveness threshold (i.e. £30,000).[74] All other strategies are dominated by either of the strategies that based diagnosis in FFA only followed by nurse led or ophthalmologist led monitoring. Diagnosis based only on OCT appears in third place combined with nurse-led monitoring. In terms of costs, the strategies' order is driven mainly by the monitoring pathway, with the lowest average total costs coming from the nurse-led monitoring pathway (1st to 3rd places), then the ophthalmologist-led (4th to 6th) and OCT only-based (7th to 9th) monitoring pathways, respectively. It should be noted, then, that the three model strategies that used OCT only as the basis for monitoring criteria were the strategies with higher average costs (Table 31). This is due to the cost of treatment, that represents 76% of the total average cost within these strategies, the highest proportion for all compared strategies (e.g. average 65% and minimum 55%).

Table 31 Base case cost-effectiveness results - men

Strategy	Cost (£)	Incremental Cost (£)	QALYs	Incremental QALYs	ICER (£)
3) FFA & Nurse	39,769	-	10.473	0.000	0
9) Ophthalmologist & Nurse	39,790	21	10.472	-0.001	-33,237
6) OCT & Nurse	41,607	1,838	10.465	-0.008	-224,403
2) FFA & Ophthalmologist	44,649	4,880	10.575	0.102	47,768
8) Ophthalmologist & Ophthalmologist	44,669	20	10.574	-0.001	-31,094
5) OCT & Ophthalmologist	47,131	2,482	10.567	-0.008	-293,938
1) FFA & OCT	62,759	18,110	10.449	-0.126	-144,229
7) Ophthalmologist & OCT	62,778	18,129	10.449	-0.126	-143,662
4) OCT & OCT	67,421	22,772	10.442	-0.133	-170,859

Notes:

1. The ICERS are calculated against the next cheapest non-dominated strategy.

Figure 15 shows the cost-effectiveness plane for the base case analysis and the nine diagnosis-monitoring combination strategies. For easier interpretation, data marker shapes relate to the diagnosis strategy, while marker filling/colour relates to the monitoring strategy. Namely, square, circle and triangle shapes are used for FFA only, OCT only, and ophthalmologist

stepwise diagnosis, respectively. In addition, black, grey and none marker fillings correspond to ophthalmologist led, nurse or technician-led and OCT only based monitoring, respectively.

Three clusters can be seen in Figure 15 according to the monitoring strategy. As such, the ophthalmologist-led monitoring strategy cluster seems to produce higher expected QALYs and slightly higher expected costs compared with the nurse or technician-led monitoring strategy. The OCT only monitoring strategy cluster results in a higher expected cost and lower expected QALYs compared with the other two monitoring strategies.

Within each of these clusters, the FFA diagnosis strategy dominates OCT only as well as the ophthalmologist stepwise diagnosis strategy (e.g. VA, OCT and SLB in all, followed by FFA if positive or unclear results). Also, to note is that the ophthalmologist diagnostic and FFA diagnostic pathways have very similar expected cost and QALYs within each cluster and, as such, data markers seem to overlap. This is due to the close values assumed for diagnosis sensitivity and specificity in these two diagnostic pathways.

Figure 15 Base case cost-effectiveness results - men

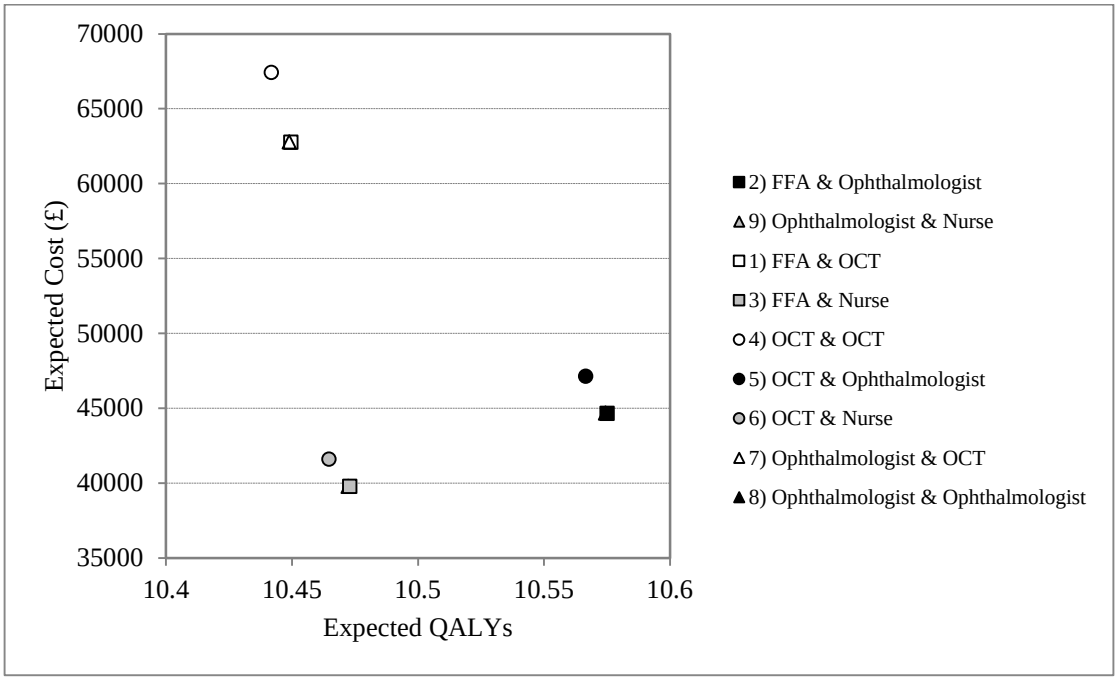


Table 32 and Figure 16 show probabilistic sensitivity analysis for the base case. Diagnosing with FFA only followed by nurse or technician-led monitoring has the highest probability of being cost-effective for up to £40,000 willingness to pay for an extra QALY. At higher threshold values (e.g. £50,000) diagnosing with FFA only followed by ophthalmologist-based monitoring has a higher probability of being cost-effective. Overall, diagnosis with FFA with

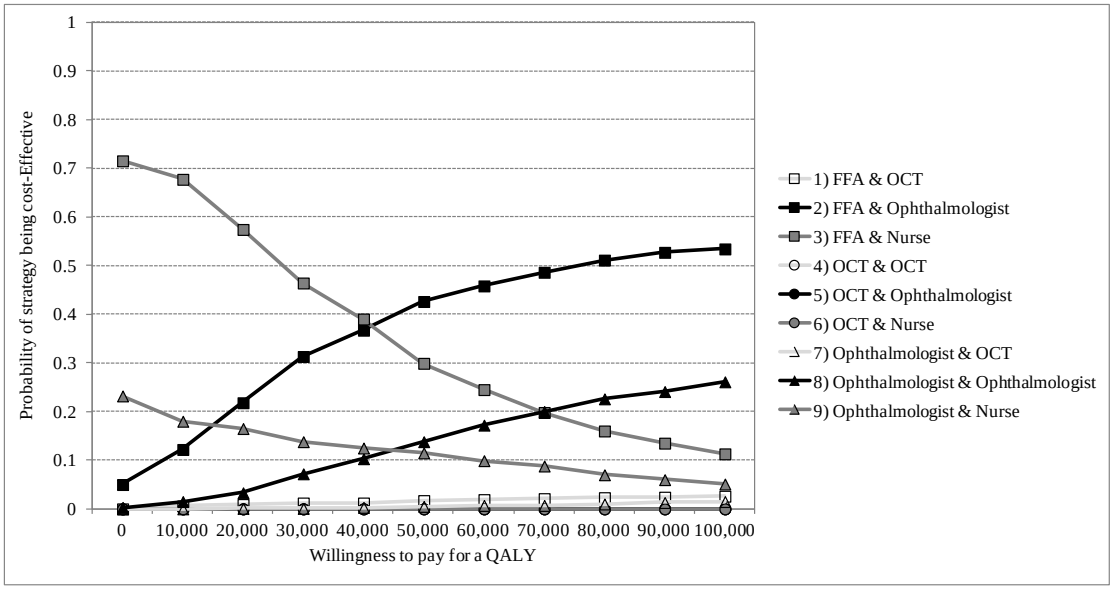
either nurse-led or ophthalmologist-led monitoring has more than a 70% chance of being cost effective at willingness to pay values for an extra QALY of between £10,000 and £50,000. These strategies lose some ground against ophthalmologist-based diagnosis (e.g. 'Ophthalmologist & Ophthalmologist' and 'Ophthalmologist & Nurse') at high levels of willingness to pay for extra QALY threshold values (Table 32 and Figure 16). At £30,000 willingness to pay for a QALY threshold value and regardless of the diagnosis pathways (e.g. FFA only, OCT only or ophthalmologist), nurse or technician-led monitoring has a 61% probability of being cost-effective.

Table 32 Probabilistic sensitivity analysis. Base case - men

Strategy	**Probability of strategy being cost-effective at alternative threshold values for society's willingness to pay for a QALY (%)**				
	£10,000	**£20,000**	**£30,000**	**£40,000**	**£50,000**
1) FFA & OCT	0.6	0.9	1.2	1.2	1.7
2) FFA & Ophthalmologist	12.2	21.8	31.3	36.7	42.6
3) FFA & Nurse	67.7	57.4	46.4	39.0	29.9
4) OCT & OCT	0.0	0.0	0.0	0.0	0.0
5) OCT & Ophthalmologist	0.0	0.0	0.0	0.0	0.0
6) OCT & Nurse	0.0	0.0	0.0	0.0	0.0
7) Ophthalmologist & OCT	0.0	0.1	0.1	0.3	0.5
8) Ophthalmologist & Ophthalmologist	1.5	3.3	7.2	10.3	13.8
9) Ophthalmologist & Nurse	18.0	16.5	13.8	12.5	11.5

Figure 16 shows that when expanding this range up to £100,000, diagnosing with FFA only followed by the ophthalmologist-based monitoring strategy will have more than a 50% chance of being cost-effective. In addition, FFA only based diagnosis strategies lose some ground against ophthalmologist-based diagnosis strategies (i.e. 'Ophthalmologist & Ophthalmologist' and 'Ophthalmologist & Nurse') at high levels of willingness to pay threshold values (Table 32 and Figure 16).

Figure 16 Cost-effectiveness acceptability curves. Base case – men



Sensitivity analysis

Using mortality rate data for women

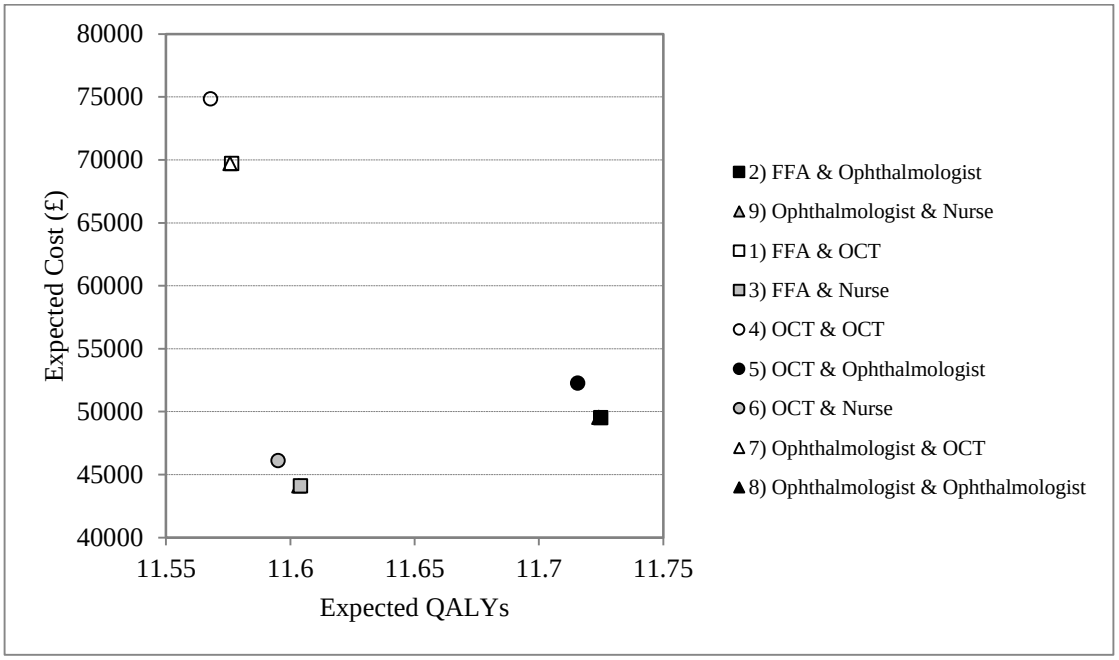
Table 33 and Figure 17 present cost-effectiveness results for women. As expected, all strategies produce more QALYs, incurring higher average costs. This is because of the longer life expectancy for women. This affects all of the model strategies in a similar manner. As such, there are no differences in the (average cost) order of the strategies or the general results compared with those for the base case analysis for men (Table 31). Diagnosing with FFA followed by nurse or technician-led monitoring is still the strategy with the lowest average cost and dominates all other compared strategies, apart from diagnosis with FFA followed by ophthalmologist-led monitoring. However, the ICER for moving to the latter strategy is above the usually accepted cost-effectiveness threshold (i.e. £30,000).[74]

Table 33 Cost-effectiveness results - women

Strategy	Cost (£)	Incremental Cost (£)	QALYs	Incremental QALYs	ICER (£)
3) FFA & Nurse	44,099	0	11.604	0.000	0
9) Ophthalmologist & Nurse	44,119	21	11.603	-0.001	-30,521
6) OCT & Nurse	46,125	2,026	11.595	-0.009	-226,433
2) FFA & Ophthalmologist	49,527	5,428	11.725	0.121	44,959
8) Ophthalmologist & Ophthalmologist	49,547	20	11.724	-0.001	-28,491
5) OCT & Ophthalmologist	52,262	2,735	11.715	-0.009	-296,276
1) FFA & OCT	69,712	20,185	11.576	-0.148	-136,016
7) Ophthalmologist & OCT	69,731	20,204	11.576	-0.149	-135,517
4) OCT & OCT	74,847	25,321	11.568	-0.157	-161,433

Similar clusters can be observed in the cost-effectiveness results for men (Figure 15) and women (Figure 17), with the three clusters depending on the monitoring care pathway (i.e. OCT only, nurse or technician-led, or ophthalmologist-led monitoring). As was the case with Figure 15, the ophthalmologist diagnostic and FFA diagnostic pathways have very similar expected cost and QALYs within each cluster and, as such, data markers seem to overlap. The Table 33 and Figure 17 results indicate that no dramatic differences can be expected for the women and men model run results. Therefore, further sensitivity analyses were conducted only for the male cohort.

Figure 17 Cost-effectiveness results - women



7.2.8 One-way sensitivity analyses

Extensive one-way sensitivity analyses were undertaken. This section reports a selected number of these, while full results are presented in Appendix 9. All one-way sensitivity analyses show results moving in the expected direction (i.e. lower sensitivity or specificity for OCT would result in OCT-based strategies being less cost-effective). Tables 34 to 38 show one-way sensitivity analysis for OCT diagnostic sensitivity and specificity, OCT monitoring sensitivity and specificity and OCT unit cost, respectively. The base case analysis results seem robust. In all reported sensitivity analyses, diagnosis with FFA combined with nurse or technician-led monitoring (based on VA and OCT with a referral to the ophthalmologist if positive or unclear) has the lowest total expected costs and dominates all others, apart from FFA for diagnosis with ophthalmologist-led monitoring. In a limited number of model runs alternative strategies stop being dominated by diagnosis with FFA followed by nurse or technician-led monitoring. However, in many of these cases the variable values used to run the analysis were extreme (see Table 34 and 36 for OCT diagnostic and monitoring sensitivities equal to 1, respectively). Results are sensitive to the value of monitoring specificity for OCT. Table 37 suggests that OCT monitoring specificity above 80% could make diagnosis with FFA combined with monitoring with OCT only, a cost-effective strategy. However, this is to almost double the specificity values reported for monitoring in chapter 6.

Table 34 One-way sensitivity analysis – OCT diagnostic sensitivity

OCT diagnostic sensitivity	Strategy	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
0.8	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	41,594	10.459	1,824	-0.014	-133,258
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	47,114	10.561	2,465	-0.014	-173,407
	1) FFA & OCT	62,759	10.449	18,110	-0.126	-144,229
	7) Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	-143,662
	4) OCT & OCT	67,394	10.436	22,745	-0.139	-163,795
0.9	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	41,611	10.466	1,841	-0.007	-270,172
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	47,135	10.568	2,486	-0.007	-355,119
	1) FFA & OCT	62,759	10.449	18,110	-0.126	-144,229
	7) Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	-143,662
	4) OCT & OCT	67,428	10.443	22,779	-0.132	-172,719
1	3) FFA & Nurse	39,769	10.473			

OCT diagnostic sensitivity	Strategy	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	41,628	10.473	1,859	0.000	31,635,704
	2) FFA & Ophthalmologist	44,649	10.575	3,021	0.102	29,593
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	47,157	10.575	2,507	0.000	11,797,675
	1) FFA & OCT	62,759	10.449	15,602	-0.126	-124,050
	7) Ophthalmologist & OCT	62,778	10.449	15,621	-0.126	-123,584
	4) OCT & OCT	67,462	10.450	20,306	-0.125	-162,290

Table 35 One-way sensitivity analysis – OCT diagnostic specificity

OCT diagnostic specificity	Strategy	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
0.55	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	43,619	10.465	3,850	-0.008	-473,564
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	49,821	10.567	5,172	-0.008	-629,095

OCT diagnostic specificity	Strategy	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
	1) FFA & OCT	62,759	10.449	18,110	-0.126	-144,229
	7) Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	-143,662
	4) OCT & OCT	72,407	10.442	27,758	-0.133	-209,343
0.6	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	43,182	10.465	3,412	-0.008	-419,079
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	49,236	10.567	4,587	-0.008	-554,702
	1) FFA & OCT	62,759	10.449	18,110	-0.126	-144,229
	7) Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	-143,662
	4) OCT & OCT	71,324	10.442	26,674	-0.133	-200,943
0.65	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	42,744	10.465	2,975	-0.008	-364,772
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	48,651	10.567	4,002	-0.008	-481,174
	1) FFA & OCT	62,759	10.449	18,110	-0.126	-144,229
	7) Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	-143,662

OCT diagnostic specificity	Strategy	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
	4) OCT & OCT	70,240	10.442	25,590	-0.133	-192,562
0.7	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	42,307	10.465	2,538	-0.008	-310,643
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	48,067	10.567	3,418	-0.008	-408,495
	1) FFA & OCT	62,759	10.449	18,110	-0.126	-144,229
	7) Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	-143,662
	4) OCT & OCT	69,156	10.442	24,507	-0.133	-184,200
0.75	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	41,870	10.465	2,100	-0.008	-256,690
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	47,482	10.567	2,833	-0.008	-336,651
	1) FFA & OCT	62,759	10.449	18,110	-0.126	-144,229
	7) Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	-143,662
	4) OCT & OCT	68,072	10.442	23,423	-0.133	-175,856
0.8	3) FFA & Nurse	39,769	10.473			

OCT diagnostic specificity	Strategy	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	41,432	10.465	1,663	-0.008	-202,914
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	46,897	10.567	2,248	-0.008	-265,626
	1) FFA & OCT	62,759	10.449	18,110	-0.126	-144,229
	7) Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	-143,662
	4) OCT & OCT	66,988	10.442	22,339	-0.133	-167,531
0.85	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	40,995	10.465	1,226	-0.008	-149,312
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	46,312	10.567	1,663	-0.009	-195,408
	1) FFA & OCT	62,759	10.449	18,110	-0.126	-144,229
	7) Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	-143,662
	4) OCT & OCT	65,904	10.442	21,255	-0.133	-159,225
0.9	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	40,558	10.465	788	-0.008	-95,884

OCT diagnostic specificity	Strategy	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	45,727	10.566	1,078	-0.009	-125,982
	1) FFA & OCT	62,759	10.449	18,110	-0.126	-144,229
	7) Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	-143,662
	4) OCT & OCT	64,820	10.441	20,171	-0.134	-150,937
0.95	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	40,120	10.465	351	-0.008	-42,629
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	45,143	10.566	494	-0.009	-57,335
	1) FFA & OCT	62,759	10.449	18,110	-0.126	-144,229
	7) Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	-143,662
	4) OCT & OCT	63,736	10.441	19,087	-0.134	-142,667
1	6) OCT & Nurse	39,683	10.465			
	3) FFA & Nurse	39,769	10.473	86	0.008	10,453
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	5) OCT & Ophthalmologist	44,558	10.566	4,789	0.094	51,214
	2) FFA & Ophthalmologist	44,649	10.575	91	0.009	10,545

OCT diagnostic specificity	Strategy	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	4) OCT & OCT	62,652	10.441	18,003	-0.134	-134,416
	1) FFA & OCT	62,759	10.449	18,110	-0.126	-144,229
	7) Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	-143,662

Table 36 One-way sensitivity analysis – OCT monitoring sensitivity

Monitoring sensitivity OCT	Strategy	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
0.9	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	41,607	10.465	1,838	-0.008	-224,403
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	47,131	10.567	2,482	-0.008	-293,938
	1) FFA & OCT	63,312	10.503	18,663	-0.072	-260,619
	7) Ophthalmologist & OCT	63,331	10.503	18,682	-0.072	-258,561
	4) OCT & OCT	67,974	10.495	23,325	-0.080	-293,337
1	3) FFA & Nurse	39,769	10.473			

	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	41,607	10.465	1,838	-0.008	-224,403
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	47,131	10.567	2,482	-0.008	-293,938
	1) FFA & OCT	64,277	10.600	19,628	0.025	788,482
	7) Ophthalmologist & OCT	64,296	10.599	19	-0.001	-28,229
	4) OCT & OCT	68,939	10.592	4,662	-0.008	-565,643

Table 37 One-way sensitivity analysis – OCT monitoring specificity

Monitoring specificity OCT	Strategy	Cost	QALYs	Incremental Cost	Incremental Effectiveness	ICER
0.3	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	41,607	10.465	1,838	-0.008	-224,403
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	47,131	10.567	2,482	-0.008	-293,938
	1) FFA & OCT	74,212	10.459	29,563	-0.116	-255,643
	7) Ophthalmologist & OCT	74,230	10.459	29,581	-0.116	-254,397
	4) OCT & OCT	80,083	10.452	35,434	-0.123	-287,514

Monitoring specificity OCT	Strategy	Cost	QALYs	Incremental Cost	Incremental Effectiveness	ICER
0.4	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	41,607	10.465	1,838	-0.008	-224,403
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	47,131	10.567	2,482	-0.008	-293,938
	1) FFA & OCT	67,780	10.454	23,130	-0.121	-190,790
	7) Ophthalmologist & OCT	67,798	10.453	23,149	-0.122	-189,953
	4) OCT & OCT	72,979	10.446	28,330	-0.129	-219,784
0.5	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	41,607	10.465	1,838	-0.008	-224,403
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	47,131	10.567	2,482	-0.008	-293,938
	1) FFA & OCT	61,521	10.448	16,872	-0.127	-133,240
	7) Ophthalmologist & OCT	61,540	10.448	16,891	-0.127	-132,734
	4) OCT & OCT	66,049	10.441	21,400	-0.134	-159,275
0.6	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237

Monitoring specificity OCT	Strategy	Cost	QALYs	Incremental Cost	Incremental Effectiveness	ICER
	6) OCT & Nurse	41,607	10.465	1,838	-0.008	-224,403
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	47,131	10.567	2,482	-0.008	-293,938
	1) FFA & OCT	55,429	10.443	10,780	-0.132	-81,774
	7) Ophthalmologist & OCT	55,449	10.443	10,800	-0.132	-81,537
	4) OCT & OCT	59,286	10.435	14,636	-0.140	-104,824
0.7	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	41,607	10.465	1,838	-0.008	-224,403
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	47,131	10.567	2,482	-0.008	-293,938
	1) FFA & OCT	49,498	10.438	4,849	-0.137	-35,432
	7) Ophthalmologist & OCT	49,518	10.438	4,869	-0.137	-35,418
	4) OCT & OCT	52,683	10.430	8,033	-0.145	-55,508
0.8	3) FFA & Nurse	39,769	10.473			
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	41,607	10.465	1,838	-0.008	-224,403
	1) FFA & OCT	43,721	10.433	3,952	-0.040	-99,944

Monitoring specificity OCT	Strategy	Cost	QALYs	Incremental Cost	Incremental Effectiveness	ICER
	7) Ophthalmologist & OCT	43,742	10.433	3,973	-0.040	-98,928
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	4) OCT & OCT	46,234	10.425	1,585	-0.150	-10,589
	5) OCT & Ophthalmologist	47,131	10.567	2,482	-0.008	-293,938
0.9	1) FFA & OCT	38,093	10.429			
	7) Ophthalmologist & OCT	38,114	10.428	21	-0.001	-34,221
	3) FFA & Nurse	39,769	10.473	1,676	0.044	37,884
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	4) OCT & OCT	39,934	10.421	164	-0.052	-3,146
	6) OCT & Nurse	41,607	10.465	1,838	-0.008	-224,403
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	47,131	10.567	2,482	-0.008	-293,938
1	1) FFA & OCT	32,608	10.424			
	7) Ophthalmologist & OCT	32,629	10.423	21	-0.001	-35,125
	4) OCT & OCT	33,776	10.416	1,168	-0.008	-144,031
	3) FFA & Nurse	39,769	10.473	7,161	0.049	146,783
	9) Ophthalmologist & Nurse	39,790	10.472	21	-0.001	-33,237
	6) OCT & Nurse	41,607	10.465	1,838	-0.008	-224,403

Monitoring specificity OCT	Strategy	Cost	QALYs	Incremental Cost	Incremental Effectiveness	ICER
	2) FFA & Ophthalmologist	44,649	10.575	4,880	0.102	47,768
	8) Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	-31,094
	5) OCT & Ophthalmologist	47,131	10.567	2,482	-0.008	-293,938

Table 38 One-way sensitivity analysis – OCT unit cost

Unit cost OCT	Strategy	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
30	9) Ophthalmologist & Nurse	37,446	10.472			
	3) FFA & Nurse	37,446	10.473	1	0.001	835
	6) OCT & Nurse	39,071	10.465	1,625	-0.008	-198,353
	8) Ophthalmologist & Ophthalmologist	42,317	10.574	4,870	0.102	47,980
	2) FFA & Ophthalmologist	42,318	10.575	1	0.001	1,398
	5) OCT & Ophthalmologist	44,586	10.567	2,268	-0.008	-268,648
	7) Ophthalmologist & OCT	60,434	10.449	18,116	-0.126	-143,560
	1) FFA & OCT	60,436	10.449	18,118	-0.126	-144,295
	4) OCT & OCT	64,885	10.442	22,567	-0.133	-169,320
40	3) FFA & Nurse	38,538	10.473			
	9) Ophthalmologist & Nurse	38,548	10.472	9	-0.001	-15,184
	6) OCT & Nurse	40,263	10.465	1,725	-0.008	-210,601

Unit cost OCT	Strategy	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
	2) FFA & Ophthalmologist	43,414	10.575	4,875	0.102	47,723
	8) Ophthalmologist & Ophthalmologist	43,423	10.574	9	-0.001	-13,878
	5) OCT & Ophthalmologist	45,783	10.567	2,369	-0.008	-280,538
	1) FFA & OCT	61,528	10.449	18,114	-0.126	-144,264
	7) Ophthalmologist & OCT	61,536	10.449	18,122	-0.126	-143,608
	4) OCT & OCT	66,078	10.442	22,664	-0.133	-170,044
50	3) FFA & Nurse	39,630	10.473			
	9) Ophthalmologist & Nurse	39,650	10.472	19	-0.001	-31,202
	6) OCT & Nurse	41,456	10.465	1,825	-0.008	-222,848
	2) FFA & Ophthalmologist	44,510	10.575	4,879	0.102	47,763
	8) Ophthalmologist & Ophthalmologist	44,529	10.574	19	-0.001	-29,154
	5) OCT & Ophthalmologist	46,979	10.567	2,469	-0.008	-292,428
	1) FFA & OCT	62,620	10.449	18,110	-0.126	-144,233
	7) Ophthalmologist & OCT	62,638	10.449	18,128	-0.126	-143,656
	4) OCT & OCT	67,270	10.442	22,760	-0.133	-170,767
60	3) FFA & Nurse	40,722	10.473			
	9) Ophthalmologist & Nurse	40,752	10.472	29	-0.001	-47,221
	6) OCT & Nurse	42,648	10.465	1,926	-0.008	-235,095
	2) FFA & Ophthalmologist	45,606	10.575	4,884	0.102	47,803
	8) Ophthalmologist & Ophthalmologist	45,635	10.574	29	-0.001	-44,429
	5) OCT & Ophthalmologist	48,176	10.567	2,569	-0.008	-304,319

Unit cost OCT	Strategy	Cost	QALYs	Incremental Cost	Incremental QALYs	ICER
	1) FFA & OCT	63,712	10.449	18,106	-0.126	-144,201
	7) Ophthalmologist & OCT	63,740	10.449	18,134	-0.126	-143,703
	4) OCT & OCT	68,462	10.442	22,856	-0.133	-171,491
70	3) FFA & Nurse	41,814	10.473			
	9) Ophthalmologist & Nurse	41,854	10.472	39	-0.001	-63,240
	6) OCT & Nurse	43,840	10.465	2,026	-0.008	-247,342
	2) FFA & Ophthalmologist	46,702	10.575	4,888	0.102	47,842
	8) Ophthalmologist & Ophthalmologist	46,741	10.574	39	-0.001	-59,705
	5) OCT & Ophthalmologist	49,372	10.567	2,670	-0.008	-316,209
	1) FFA & OCT	64,805	10.449	18,102	-0.126	-144,170
	7) Ophthalmologist & OCT	64,842	10.449	18,140	-0.126	-143,751
	4) OCT & OCT	69,655	10.442	22,953	-0.133	-172,214

Scenario analysis

Scenario analysis favouring the OCT test was conducted to explore conditions under which OCT only based strategies could become cost-effective. The scenarios are described in section 7.2.6 and the input data used reported in Table 30. Best possible OCT test sensitivity and specificity were incorporated into the model. In addition, the lowest possible unit cost for OCT and a higher assumed unit cost value for FFA were used. Scenario 2 differs in the unit cost assumed for each treatment injection (£50) and scenario 3 explores community monitoring (e.g. unit cost for OCT as for community optometrist and an ophthalmologist visit cost added only when treatment was needed). Tables 39 to 41 show the scenario analysis results. For scenario 1 (Table 39) and scenario 3 (Table 41) strategies that based their diagnosis or monitoring decisions on OCT test results only are dominated (i.e. have higher expected costs and lower expected QALYs). It should be noted that, due to the lower unit cost for the OCT test, the strategy with the lower expected cost is diagnosis by an ophthalmologist combined with nurse or technician-led monitoring.

Table 39 Scenario analysis 1

Strategy	Cost (£)	Incremental Cost (£)	QALYs	Incremental QALYs	ICER (£)
9) Ophthalmologist & Nurse	36,320	-	10.478		
3) FFA & Nurse	36,707	387	10.471	-0.007	-54,280
6) OCT & Nurse	37,417	1,097	10.470	-0.008	-140,873
8) Ophthalmologist & Ophthalmologist	41,284	4,964	10.579	0.101	49,012
2) FFA & Ophthalmologist	41,740	456	10.573	-0.006	-73,232
5) OCT & Ophthalmologist	42,781	1,497	10.573	-0.007	-218,869
7) Ophthalmologist & OCT	48,241	6,957	10.536	-0.043	-161,687
1) FFA & OCT	48,791	7,507	10.530	-0.050	-151,253
4) OCT & OCT	50,273	8,989	10.529	-0.050	-179,277

Table 40 shows results for scenario 2 (i.e. the same input data as for scenario 1 but assuming cost of treatment of £50 per injection). The pathway strategy with the lowest cost is the ophthalmologist stepwise diagnosis followed by monitoring decisions based on OCT only. The next costly strategy is the one that based the diagnosis decision on FFA only and the monitoring

treatment decision on OCT test results only. However, this strategy is dominated by the former. The next non-dominated strategy was diagnosis by an ophthalmologist followed by an ophthalmologist led monitoring (e.g. 'Ophthalmologist & Ophthalmologist') with an ICERs of £19,917. This is within the usual £30,000[74] threshold and potentially worthwhile to adopt. The Table 40 results indicate that OCT strategies could become cost-effective if the cost of treatment was lower. In terms of the economic model, this would be a lower penalisation for those strategies that treat individuals who do not need to be treated (i.e. those tests or strategies that result in lower specificity and therefore a higher number of false positive results).

Table 40 Scenario analysis 2

Strategy	Cost (£)	Incremental Cost (£)	QALYs	Incremental QALYs	ICER (£)
7) Ophthalmologist & OCT	13,983	-	10.536		
1) FFA & OCT	14,158	175	10.530	-0.007	-26,423
4) OCT & OCT	14,583	600	10.529	-0.007	-84,256
8) Ophthalmologist & Ophthalmologist	14,840	857	10.579	0.043	19,917
2) FFA & Ophthalmologist	15,024	184	10.573	-0.006	-29,567
5) OCT & Ophthalmologist	15,477	636	10.573	-0.007	-93,000
9) Ophthalmologist & Nurse	15,601	761	10.478	-0.101	-7,511
3) FFA & Nurse	15,790	949	10.471	-0.108	-8,757
6) OCT & Nurse	16,218	1,377	10.470	-0.109	-12,627

Table 41 Scenario analysis 3

Strategy	Cost (£)	Incremental Cost (£)	QALYs	Incremental QALYs	ICER (£)
9) Ophthalmologist & Nurse	36,320	-	10.478	0.000	0
3) FFA & Nurse	36,707	387	10.471	-0.007	-54,280
6) OCT & Nurse	37,417	1,097	10.470	-0.008	-140,873
8) Ophthalmologist & Ophthalmologist	41,284	4,964	10.579	0.101	49,012
2) FFA & Ophthalmologist	41,740	456	10.573	-0.006	-73,232
5) OCT & Ophthalmologist	42,781	1,497	10.573	-0.007	-218,869
7) Ophthalmologist & OCT	43,527	2,243	10.536	-0.043	-52,132
1) FFA & OCT	44,018	2,734	10.530	-0.050	-55,084
4) OCT & OCT	45,257	3,974	10.529	-0.050	-79,247

7.2.9 Summary and discussion

This chapter reported on a systematic review of economic evaluations and a model-based economic evaluation of alternative strategies for the diagnosis and monitoring of individuals with nAMD. No studies identified in the literature met the inclusion criteria for the systematic review.

Nine strategies (combinations of three different diagnostic and monitoring pathways) were considered within the economic model. The strategies used to a different extent OCT for diagnosis and/or monitoring of nAMD individuals. Extensive deterministic and probabilistic sensitivity analyses were conducted. The strategy that based its diagnosis decision on the results of FFA only, combined with VA and OCT interpreted together by a nurse or technician as the first monitoring step, with a referral to an ophthalmologist if the first monitoring assessment was positive or unclear ('FFA & Nurse'), had the lowest expected total cost. This strategy dominated (i.e. lower expected costs and higher expected QALYs) all others apart from one: diagnosis with FFA only, combined with monitoring by an ophthalmologist ('FFA & Ophthalmologist'). The 'FFA & Nurse' and 'FFA & Ophthalmologist' strategies had, respectively, a 46.5% and 29.8% probability of being cost-effective at the £30,000 threshold value of willingness to pay for an extra QALY. In addition, the 'FFA & Nurse' strategy dominated all others in the great majority of sensitivity analyses.

The strategies that used OCT only for their monitoring decisions were in almost every model run ordered last in terms of total expected cost and were often dominated by others. The strategy that used OCT only for both diagnosis and monitoring decisions was in almost every model run the most costly strategy.

Scenario analysis was conducted in order to explore the conditions under which an OCT only strategy would become cost-effective. Three scenarios were developed using the best test performance data for OCT combined with a lower cost for OCT (£20.90) and a higher cost for FFA (£137). Scenario 2 added to this a lower unit cost for treatment (e.g. equivalent to the cost of bevacizumab, £50, instead of the £742 cost of ranibizumab considered for the base case analysis). This scenario showed the ophthalmologist stepwise pathway for diagnosis combined with OCT only for monitoring, to be, on average, the least costly strategy. Alternative strategies were either dominated (i.e. more costly and produced fewer QALYs) or the resulted ICER was well above the usual threshold accepted for policy decisions.[74] This was an expected result. The low OCT specificity for monitoring in these scenarios and in the base case (0.61 and 0.44, respectively) meant that a high number of positive results would actually be false positives. The lower cost of treating individuals who do not need to be treated reduced the model penalisation for the OCT only based strategies and therefore improved their cost-effectiveness.

Best practice guidelines were followed for this model-based economic evaluation exercise.[74,82] In spite of this, these results should be interpreted with caution. A considerable effort was made to retrieve the best available test or assessment performance data by conducting a systematic review of the literature. Other data were obtained from focused but reproducible searches. Nevertheless, there is an inherent problem with model-based economic evaluations that incorporate evidence from several sources, even when these data have been obtained systematically. The limitations of the SD-OCT performance data incorporated into the economic model have been mentioned in chapter 6, with only two and three studies, respectively, contributing to the diagnosis and monitoring performance data. Moreover, while OCT diagnosis and monitoring performance data were retrieved from a systematic review of the literature, no such data were available for the strategies involving diagnosis or monitoring assessment by an ophthalmologist or monitoring assessment by a nurse or technician. Therefore, these data for the model were obtained from expert opinion. This constitutes a major caveat of the analysis and further research in this area is needed.

This economic model needed to consider individuals' disease status (i.e. active or inactive nAMD) as well as test results on a monthly basis. In addition, these had to be combined with alternative visual acuity states in order to incorporate to utility weights into the model. It was

felt that considering the effect of a fellow eye status (VA and nAMD status) would add major complexity to the model without a great deal of benefit from such incorporation. This is the most common approach used among economic models in this health area but constitutes a limitation of the current study. Utility weights used were obtained from nAMD individuals and grouped according to visual acuity in the better-seeing eye. It is believed that this would better reflect individuals' health status. However, the clear limitation of 'one eye models' is the underestimation of resources used. A proportion of monitored nAMD individuals will have this condition in both eyes instead of one, and, had the disease been active, would be receiving treatment injections in each eye. Intuitively, this would increase the treatment cost for those strategies with a higher number of (true and false) positive results (i.e. higher sensitivity and lower specificity) and hence would be unlikely to modify the overall conclusions of this economic evaluation.

The model did not consider effects on utility due to treatment injections. Anxiety in nAMD individuals was believed to occur at each monitoring visit mainly due to the uncertainty of the underlying condition (i.e. whether or not nAMD was active) and not the effects of the treatment injections. No evidence was obtained on this issue in spite of focused searches. Further research in this area is needed. Utility weight decrements from treatment adverse effects were included and this might partially overcome the above-mentioned potential limitation.

Limited evidence was available on the probability of nAMD active individuals becoming inactive when under treatment or inactive nAMD individuals becoming active. Data were retrieved from the literature and also from a UK-based RCT.[9] Survival data were received from the IVAN study [personal communication - Dr Chris Rogers, 12th June 2013] on first re-treatment failure criteria (i.e. inactive individuals who needed to be re-treated). These were used to develop model parameter values for the first year of the model run. There were no such data available for further failures and we had to rely on the available limited data from the literature[69] or on expert opinion for year 2 onwards. In addition, progression data on visual acuity were based on the two year follow-up MARINA study.[68] All of these were relatively short term follow-up studies (around two years) but used to inform model parameters for a lifetime time horizon. These are clear limitations of the model and therefore its results should be interpreted with caution. Further research investigating individuals' nAMD active/inactive status (e.g., probability of disease changing from inactive to active) would be desirable.

7.2.10 Conclusions

A strategy that based its diagnostic decision on the results of FFA only, combined with VA and OCT interpreted together by a nurse or technician as a first monitoring step, with a referral to an ophthalmologist if this first monitoring assessment was positive or unclear, had the lowest expected total cost. This strategy had a 46.5% probability of being cost-effective at a £30,000 threshold value of willingness to pay for an extra QALY. In addition, this strategy dominated all others apart from one (i.e. diagnosis with FFA combined with ophthalmologist-led monitoring) in the great majority of sensitivity analyses. Strategies that used OCT test results alone to make diagnosis or monitoring treatment decisions were unlikely to be a cost-effective use of resources. This result seemed to be driven by the OCT low specificity that resulted in a high number of false positive results. The present analysis indicated that a further refinement of monitoring (i.e. a further monitoring step other than OCT alone) seemed desirable.

These results should be interpreted with caution. The economic model would benefit from further research to better inform a number of model parameter values. Studies that investigate the likelihood of nAMD individuals becoming active or inactive after subsequent treatments are desirable. In addition, a preference-based health status and process of care valuation study to explore the effects of treatment injections on individuals' utility weights is needed. Finally, a comparative study to establish the performance of the ophthalmologist-based strategy compared with the nurse or technician-based strategy for monitoring individuals with nAMD is required to inform future economic models in this area.

8 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

The introduction of OCT and other diagnostic technologies for diagnosis and monitoring of patients with nAMD has a range of implications for the NHS, patients and other parties. There has already been a shift in the diagnostic pathway for this group of patients caused by the adoption of OCT, rather than the previously used FFA, as a method of establishing the diagnosis and of evaluating disease activity. There are consequential effects not only on patient outcomes but also on service delivery, health care professionals and wider society of this change in preferred diagnostic technologies used.

8.1 Factors relevant to the NHS

8.1.1 Estimating the numbers of patients with nAMD

A summary of the epidemiology of nAMD has been described in this study. In brief, the prevalence and incidence of nAMD and the consequent burden to the NHS will increase over the next few decades because of the ageing population. By 2060, mean life expectancy will grow by 8.5 years for men (to 84.5 years) and 6.9 years for women (to 89.0 years).[83]

8.1.2 Implications for service provision

The clinical workload associated with the frequent follow-up required for patients with nAMD is substantial. As more new patients are diagnosed and the population continues to age, the patient population will continue to increase. It is thus vital that clinical services continue to adapt so that they can provide a fast and efficient service for patients with nAMD.

There are still challenges and questions about whether ophthalmology departments have sufficient capacity and the means to offer relevant testing and treatments within adequate timescales. Local diagnostic pathways require updating and assessment to ensure compliance with national guidelines e.g., to detect recurrence of active disease in these subjects. Occasional local disruptions may occur if OCT equipment suffers technical failures.

In 2012 Amoaku et al. published a document entitled “Action on AMD” that was developed by eye healthcare professionals and patient representatives with the intention of highlighting the urgent and continuing need for change within wet AMD services.[55] This document also provided examples of good practice and service development, including the possibility of involving other health care professionals and using OCT in the community.

8.1.3 Considerations regarding the performance of OCT for diagnosis and monitoring

At the diagnostic stage OCT is currently used in addition to FFA to provide a baseline that will be used for comparisons during the monitoring stage.

For monitoring, OCT has virtually replaced FFA in most NHS units.[84] During follow-up, monitoring also includes visual acuity testing. There is larger variability in the adoption of other tests and perceived need for FFA during follow-up. The replacement of FFA is probably due to the convenience of OCT (e.g. non-invasive, user friendly, quick, efficient). However, expert clinicians recognise the difficulty of interpreting FFA and OCT in patients with previously treated nAMD who often develop atrophic changes. The low specificity of OCT observed in this study would suggest that OCT alone should not be used for monitoring.

Another consideration is the evolving technology. For example, theoretically an increased sensitivity and specificity of new versions or novel technologies (SD-OCT) would lead to more patients being correctly diagnosed with active nAMD, and fewer wrongly diagnosed as having no active disease. This review did not find sufficient evidence on the performance of SD-OCT and it is unclear if it is superior than TD-OCT.

Regarding cost implications, there will be little cost implications for procuring and maintaining OCT equipment because most centres already use this technology. While many units will already have access to the new SD-OCT equipment, other centres may have to upgrade the current TD-OCT (e.g., purchase or lease new SD-OCT equipment).

There may be a need for training ophthalmology staff to ensure adequate technical skills to interpret the OCT scans. There is a learning curve to interpreting OCT images, especially in relation to those patients who are being monitored after treatment. Adequate quality control and quality assurance programmes would be needed in order to maintain high standards of interpretation.

8.2 Factors relevant to patients and other parties

A highly specific test may reduce the number of patients undergoing unnecessarily treatment with anti-VEGF injections, avoiding the associated discomfort, side effects and possible complications. Using OCT alone for diagnosis or monitoring would be associated with a number of false positives and unnecessary treatments. From the efficiency point of view, a specificity of at least 80% would be required for a monitoring strategy using OCT alone to be cost-effective.

From a patient preference point of view, if the diagnostic performance were adequate, it is likely that patients would prefer OCT when compared with FFA because of the unpleasantness of the latter procedure.

Monitoring in the community would be a positive development for patients and carers, who would have less distance to travel to access OCT testing. This may be possible as OCT is becoming increasingly used by community optometrists but would need to be associated with another test (e.g. visual acuity). Local arrangements and financial support would need to be put in place as community optometrists would need to be trained and reimbursed for their services. Community optometrists should also be able to communicate their findings in a timely and efficient way to clinicians in secondary care. However, inequalities in access may arise as people from disadvantaged socio-economic backgrounds may be reluctant to attend private community optometrists.

9 DISCUSSION

9.1 Diagnostic accuracy

9.1.1 Statement of principal findings

Diagnostic studies

Twenty-two diagnostic studies were included (20 full-text papers, two abstracts) involving over 2000 participants. The studies reported the performance of OCT (13 studies;), ICGA (eight studies), PHP (three studies), colour fundus photography, Amsler grid and FAF (one study each) in the detection of nAMD. Studies that reported true and false positive and negative results or provided information that allowed these data to be calculated were considered for inclusion in pooled estimates (meta-analyses), which were performed with eye as the unit of analysis.

Full-text papers were assessed for risk of bias using the QUADAS-2 tool. The domains with the greatest number of studies judged to be at high risk of bias were the patient selection domain (55%, 11/20), for reasons such as inappropriate exclusions and pre-selection of participants, and the flow and timing domain (40%, 8/20), for reasons such as the length of time between the index test and the reference standard being longer than one week, and not all participants being included in the analysis. In the index/comparator test domain and reference standard domain the risk of bias was judged to be unclear in around half of the studies [50% (10/20) and 60% (12/20) respectively]. However, all of the studies were judged to be of low concern in terms of their applicability to the review question.

Only four OCT diagnostic studies (all TD-OCT) provided sufficient data for inclusion in a meta-analysis. The pooled sensitivity and specificity (95% CI) for all OCT was moderately high at 88% (46% to 98%) and 78% (64% to 88%) respectively.

Of the other tests of interest, median sensitivity [range] was similarly high for ICGA (93.2% [84.6% to 100%]; four studies) and FAF (93.3%; one study), followed by PHP (81.5% [50.0% to 84.8%]; three studies) and colour fundus photography (70.0%; one study) and was lowest for Amsler Grid (41.7%; one study). Specificity was highest for colour fundus photography (95%; one study), followed by PHP (84.6% and 87.7%; two studies), and was similarly low for FAF (37.1%; one study) and ICGA (36.8%; one study).

Two studies reported test combinations. For OCT plus colour fundus photography, sensitivity was moderate at 74.1%, with specificity high at 92.0%. For colour fundus photography plus visual acuity sensitivity was low at 53.0% but again specificity was high at 94.0%.

Monitoring studies

Eight monitoring studies were included (all full-text) involving over 400 participants. Seven reported the performance of OCT (three TD-OCT, three SD-OCT, one both types) and one the performance of ICGA in the detection of nAMD activity. As with the diagnostic studies, the QUADAS-2 domains with the greatest number of monitoring studies judged to be at high risk of bias were the patient selection domain (25%, 2/8) and flow and timing domain (25%, 2/8), for similar reasons to those reported above. In the index/comparator test domain and reference standard domain the risk of bias was judged to be unclear in 50% (4/8) and 37.5% (3/8) of studies respectively. Similar to the diagnostic studies, all of the monitoring studies were judged to be of low concern in terms of their applicability to the review question.

Four of the OCT studies provided sufficient data for inclusion in a meta-analysis. The pooled sensitivity (95% CI) for all OCT was moderately high at 85% (72% to 93%) but with low specificity at 48% (30% to 67%). For TD-OCT, the pooled sensitivity and specificity was moderate at 70% (56% to 80%) and 65% (48% to 79%) respectively. It was not possible to calculate pooled estimates for the two SD-OCT studies using hierarchical summary receiver operating characteristic (HSROC) methodology due to insufficient data. These studies reported sensitivities of 94%[29] and 90%[15] and specificities of 27% [29] and 47%.[15] These results broadly reflect those of the diagnostic studies in terms of SD-OCT having higher sensitivity but lower specificity than TD-OCT. In particular the specificity of the SD-OCT monitoring studies was quite low.

Other than OCT, one study reported ICGA, with sensitivity of 75.9% and specificity of 88.0% for the detection of active nAMD.

9.1.2 Strengths and limitations of the assessment

In terms of strengths, a comprehensive literature search was undertaken and non-English language studies were included. Risk of bias was assessed using a modified QUADAS-2 questionnaire, tailored to the needs of this review. A HSROC model was used for the analysis, which takes account of the trade-off between true/false positives and models between-study heterogeneity.[85] The evidence for diagnosis and monitoring was considered separately. In addition to the pooled estimates for all OCT, separate pooled estimates were undertaken for TD-OCT and SD-OCT, but for SD-OCT it was not possible to use HSROC methods.

There was a very limited amount of evidence available for evaluating the diagnostic and monitoring performance of SD-OCT (and limited evidence for the performance of TD-OCT with regard to its role in surveillance monitoring of those previously diagnosed with nAMD. Although this review considered a number of alternative tests, only a few of these were reported by studies that met our inclusion criteria. There was insufficient information to address the questions of (1) the clinical effectiveness of OCT compared with FFA, (2) the acceptability of the tests and (3) the performance of other health professionals compared with ophthalmologists in interpreting OCT findings.

9.1.3 Uncertainties

Reference standard

FFA interpreted by an ophthalmologist was our reference standard test and as such was assumed to have perfect sensitivity and specificity for the detection of active nAMD. Therefore it was not possible to address the question of whether OCT might actually have better sensitivity or specificity than FFA; the optimal judgement that could have been made about OCT was that it had equally high sensitivity and specificity as FFA. In fact although OCT did have very high sensitivity the specificity for diagnosis and monitoring was suboptimal.

Glasziou et al.[86] considered the question of when a new test should replace the existing reference standard. They suggested that this might be determined by a 'fair umpire' test applied to the cases where the new test and reference standard differed. This third test, although potentially less accurate than either the new test or reference standard, could be considered a fair umpire, if its errors were considered to be independent of the other tests, although it was acknowledged that this would usually be difficult to demonstrate. Possible umpires suggested included causal exposures, concurrent testing, prognosis, or response to treatment. Glasziou et al.[86] argued that using this approach, the umpire test might be able to distinguish which test was the better reference standard. An example given was that of a new test for tuberculosis, with the tuberculin skin test as the reference standard, interferon-γ enzyme-linked immunospot (ELISpot) assays as the new test and tuberculosis exposure as the fair umpire.[86] However none of the studies included in our review provided a sufficient level of information to allow such a 'fair umpire' approach to be applied.

False positives

Excluding studies where information was only available for detection of phenotypes,[33,36,37,51] specificity for OCT was reported by six[15,27,29,31,44,52] of seven monitoring studies but only four[26,39,45,48] of ten diagnostic studies.

As already reported, specificity for OCT for diagnosis was only moderate and for monitoring was lower, with a large number of false positive results. A few studies provided some additional information on their false positive results, with suggested reasons for these including the presence of a disciform scar with persistent cystic cavities,[44] an increase in the central subfield measurement,[26] drusen/atrophy ,[45,48] cystoid abnormalities ,[15] subretinal fluid being detected before FFA leakage was observed,[39] and the detection of remnants of intraretinal fluid that had not yet been resorbed even though the underlying CNV was no longer actively leaking fluid .[31] Do et al.[26] suggested that SD-OCT may have lower specificity for the detection of CNV compared with TD-OCT because it is more likely to detect structural changes in the retina, which may be a normal anatomic variant and not necessarily representative of secondary changes in the retina owing to CNV.

Sandhu et al.[45] noted that the OCT false positive rate was reduced with the addition of stereo colour images (separate test). In current practice OCT is typically associated with visual acuity data which may improve the specificity of the test.

In two of the monitoring studies[15,29] participants had been treated with anti-VEGF therapy while in five[27,31,44,52] they had been treated with PDT. For all OCT, median sensitivity was similar across the anti-vascular endothelial growth factor (anti-VEGF) (90%) and photodynamic therapy (PDT) (88%) groups of studies, while median specificity was slightly higher across the PDT studies (51%) compared with the anti-VEGF studies (43%) It is possible that following treatment with PDT there is less likelihood of having fluid in the retina than following therapy with anti-VEGF, as fluid is a common feature in eyes treated with anti-VEGF, even after many sessions of treatment. Currently PDT is rarely used for nAMD, but the reviewed literature reflects this older modality of treatment. OCT (especially the newer version with the highest resolution, SD-OCT) may detect fluid, even when only a small amount is present and it does not necessarily relate to CNV activity (e.g. fluid may be present if there is RPE dysfunction/damage as a result of the disease or its treatment, as in normal circumstances RPE pumps fluid out of the retina). Therefore it is possible that there might be more OCT false positives resulting in lower specificity for detecting active nAMD following anti-VEGF compared with PDT treatment.

In two diagnostic studies, by Kozak et al.[35] and Reichel et al.[43] some patients were classed as having nAMD who were negative on FFA but positive on one of the other tests being assessed (13/541 eyes by TD-OCT in the Kozak study[35] and 4/20 participants by ICGA in the Reichel study).[43] For the purposes of this review these cases were considered to be test false positives (as the reference standard of FFA was considered to have perfect sensitivity and specificity). However, in some cases (e.g., with retinal haemorrhage) it is possible that ICGA may be better than FFA in detecting nAMD.

Heterogeneity across the studies

Other than the fact that one group of studies was concerned with initial diagnosis of nAMD and another with monitoring of those previously diagnosed, there were a number of other differences across the studies. In terms of differences across the participant groups, the prevalence of nAMD in the diagnostic studies ranged from 17.2% to 100% (median 80.0%) and of active nAMD in the monitoring studies from 49.2% to 83.3% (median 57.9%). The proportion of participants classed as having specific nAMD phenotpyes (e.g. classic CNV, occult CNV) varied across the studies. In eight diagnostic studies and one monitoring study participants were judged to have been pre-selected.

Detection of phenotypes

Twelve studies (eight diagnostic,[24,32,33,36,37,40,45,48] four monitoring[15,29,31,51]) reported the sensitivity of OCT in the detection of nAMD phenotypes (predominantly classic, minimally classic, occult or retinal angiomatous proliferation (RAP)). None of the studies reported detection of idiopathic polypoidal choroidal vsculopathy (IPCV). Results were mixed, and overall there was insufficient evidence to understand whether the performance of OCT differs among the different phenotypes. The monitoring study by Giani et al[29] (SD-OCT) reported high sensitivity for the detection of both classic and occult CNV activity (90.9% and 100% respectively).

Across four (TD-OCT) diagnostic studies[24,33,36,37] reporting detection of RAP the median (range) sensitivity was 65% (50% to 100%). Of the monitoring studies, Khurana et al.[15] reported higher sensitivity for SD-OCT (59%) compared with TD-OCT (35%) for detecting retinal cystoid abnormalities, while van de Moere et al.[51] reported poor sensitivity for SD-OCT for detecting cystoid macular oedema (23%) and pigment epithelial detachment (6%).

Unit of analysis issues

Twelve OCT studies used one eye per patient in the analysis.[24,26,32-37,39,44,45,48] In three of these studies[24,26,39] the inclusion criteria stipulation for the fellow eye meant that only one (study) eye

per subject was eligible for analysis. In the remaining studies the inclusion criteria were such that both eyes of some subjects might have been potentially eligible.[15,35,36,40,44,45] Of these, however, only the study by van de Moere et al.[51] reported the method used for selecting the study eye in the event of such a situation, stating that if both eyes were eligible one eye was randomly chosen for analysis. It was unclear from the other studies whether only one eye per subject had met the inclusion criteria or whether for some subjects both eyes were eligible but only one was selected.

In six OCT studies both eyes of some participants met the inclusion criteria and were included in the analysis;[15,35,36,40,44,45] however none of these studies mentioned the issue of the possible influence that the non-independence of the fellow eye might have on the analysis.

All studies included in the meta-analyses used one eye per subject, apart from the study by Sandhu et al.[45] (meta-analysis of diagnostic studies) and the study by Khurana et al.[15] (meta-analysis of monitoring studies). In the study by Sandhu et al[45] 131 eyes of 118 patients were included in the analysis, as 13 patients had bilateral activity. In the study by Khurana et al.[15] 59 eyes of 56 patients were included in the analysis, as three patients had received anti-VEGF treatment for nAMD in both eyes. These studies did not report whether any adjustment had been made to take account of the non-independence of the fellow eye and contained an insufficient level of detail to allow for an exploration of this issue. However the potential impact of fellow eye non-independence would probably be minor, at most, given the small number of subjects in the two studies for whom both eyes were included in the analysis.

9.1.4 Other relevant factors

Ongoing studies

No ongoing studies were identified of OCT or alternative tests of interest compared with a reference standard of FFA for the diagnosis, monitoring and guiding of treatment for nAMD.

Comparison of our results with other systematic reviews/HTAs

Our searches identified four HTA reports that included an assessment of OCT in the detection of nAMD.[12,87-89] The German HTA report by Sturzlinger et al,[88] (report summary in English, full-text in German) published in 2007, considered head-to-head comparisons between OCT and FFA for newly presenting patients. Eight studies were included, of which three were included in our review.[32,34,45] The other five studies did not meet our inclusion criteria (assessment of retinal pigment epithelial tear,[90] retinal pigment epithelial detachment,[91] drusen,[92] geographic atrophy,[93] and no diagnostic outcomes reported).[94] The report's

conclusions were that although OCT yielded diagnostic findings in addition to FFA results, OCT could not replace FFA during the primary diagnostic procedure.

The Belgian Health Care Knowledge Centre report by van den Bruel et al,[889] published in 2008, considered five ophthalmic tests in clinical practice, including OCT. The assessment identified the German HTA report and included an additional three studies,[27,36,44] all three of which were included in our review. The review considered FFA as the reference standard for neovascular AMD, and, similar to our review, reported high sensitivity (96-97%) and moderate specificity (66%) of OCT in detecting choroidal neovascularisation.

In the Australian MSAC report,[87] published in 2009, OCT was compared a) with FFA or clinical observation in the diagnosis of macular diseases; b) in addition to FFA and clinical examination in the monitoring of patients with macular diseases; c) in addition to computerised perimetry and clinical examination in the diagnosis of glaucoma; and d) in addition to computerised perimetry and clinical examination in the monitoring of patients with glaucoma. Regarding the diagnostic accuracy of OCT for AMD, the MSAC report concluded that due to the absence of a valid reference standard, the diagnostic accuracy of OCT for the detection of macular abnormalities could not be assessed. This approach contradicted our study, the German and Belgian HTA reports and also current practice in the UK where FFA is considered the reference standard for the diagnosis of nAMD.

In the evidence-based analysis by the Medical Advisory Secretariat, Ontario, Canada,[12] published in 2009, OCT was compared with the reference standard of FFA for AMD and diabetic macular oedema. The evaluation summarised the German HTA report and the study by Sandhu et al[45] that was also included in our review. This report also questioned the validity of FFA as a reference standard and presented conclusions that were based on expert consultations.

Aflibercept

In May 2013 NICE published final draft guidance recommending aflibercept solution for injection as an option for treating nAMD. Full guidance is expected to be published in July 2013. The treatment and monitoring schedule for this drug differs from that of ranibizumab. According to the summary of product characteristics for aflibercept, treatment should be given monthly for three consecutive 2 mg doses, followed by one injection every two months, with no need for monitoring between injections. After the first 12 months of treatment, the treatment interval may be extended based on visual and anatomic outcomes, with the schedule for monitoring determined by the treating doctor. It terms of the economic model, extending the

length of time between monitoring visits would reduce the cost associated with monitoring as well as the number of treatment courses needed. However, this would be expected to affect all model strategies in a similar manner and therefore would be unlikely to modify the general conclusions from the economic analysis. This might nevertheless reduce the cost associated with treatment and monitoring of nAMD patients for the NHS.

Future technological developments

It is likely that future technological developments in OCT will be introduced. Most OCT devices create cross-sectional images of the retina. En-face OCT technology is an emerging imaging technique derived from SD-OCT that creates images of frontal sections of retinal layers that are compatible with conventional fundus images.

Another emerging technique is OCT angiography, which uses high-speed Fourier-domain OCT for non-invasive three-dimensional imaging of the vasculature and blood flow at the posterior part of the eye.

9.2 Cost-effectiveness

9.2.1 Statement of principal findings

No studies met the inclusion criteria for the systematic review of economic evaluations as none compared diagnostic or monitoring strategies for individuals with nAMD.

Nine strategies that used to a different extent OCT for diagnosis and/or monitoring of nAMD individuals were considered within the Markov cohort economic evaluation model. The strategy that based its diagnosis decision on the results of FFA only, combined with VA and OCT interpreted together by a nurse or technician as the first monitoring step, with a referral to an ophthalmologist if the first monitoring assessment was positive or unclear ('FFA & Nurse'), had the lowest expected total cost. This strategy dominated (i.e. lower expected costs and higher expected QALYs) all others apart from one: diagnosis with FFA only, combined with monitoring by an ophthalmologist ('FFA & Ophthalmologist'). The 'FFA & Nurse' and 'FFA & Ophthalmologist' strategies had, respectively, a 46.5% and 29.8% probability of being cost-effective at the £30,000 threshold value of willingness to pay for an extra QALY. In addition, the 'FFA & Nurse' strategy dominated all others in the great majority of sensitivity analyses.

The strategies that used OCT only for their monitoring decisions were in almost every model run ordered last in terms of ascending total expected cost and were often dominated by others.

The strategy that used OCT as its only criteria for diagnosis and monitoring decisions was in almost every model run the most costly strategy.

Results were sensitive to the unit cost of treatment injections. A scenario with a lower unit cost for treatment (e.g. £50, equivalent to the cost of bevacizumab, instead of £742 considered for the base case analysis) resulted in the FFA only for diagnosis combined with OCT only for monitoring strategy having the lowest total expected cost. Alternative strategies were either dominated or had an ICER well above the usual threshold stated for cost-effectiveness (i.e. £30,000).

9.2.2 Strengths and limitations of the economic assessment

The major strength of the economic evaluation is that it attempted to use the best available evidence with the compared strategies developed from extensive discussions within the project team and advisory group. Best practice guidelines were followed for this economic evaluation exercise.[74] For instance, test performance data were obtained from the systematic review of the literature with other data retrieved from focused but reproducible searches. There is, however, an inherent problem with model-based economic evaluations that incorporate evidence from several sources, even when these data have been retrieved systematically.

The economic model needed to consider individuals' disease status (i.e. active or inactive nAMD) as well as test results on a monthly basis. In addition, these had to be combined with alternative visual acuity states in order to incorporate utility weights into the model. It was felt that considering the effect of fellow eye status (VA and nAMD status) would add major complexity to the model without much benefit from this incorporation. A clear limitation of the so-called 'one eye models' is the underestimation of resources used. A proportion of nAMD individuals will have this condition in both eyes instead of one eye and would need treatment injections in each eye should the disease be active. In the current model this would increase the cost for those strategies with higher numbers of false positives (i.e. lower specificity) and therefore would be unlikely to modify the general conclusions of this study. A 'one eye model' has also been adopted by other teams involved in economic evaluations in this health area.[60]

The model did not consider effects on utility due to treatment injections. Anxiety in nAMD individuals was believed to occur at each monitoring visit mainly due to the uncertainty of the underlying condition (i.e. active or inactive nAMD) and not the effects of the treatment injections. No evidence was obtained on this from the utility weight searches. However, utility weight decrements from adverse effects as a result of the treatment were included and this might

partially overcome the above-mentioned potential limitation. The model did not consider factors relating to patient experience of alternative monitoring schemes. As such, there was no consideration of the process of care on patient preferences and only the effect of visual acuity and the adverse effects of treatment on individual utility were incorporated into the model.

Limited evidence was available on the probability of nAMD active individuals becoming inactive when under treatment or inactive nAMD individuals becoming active. Data were retrieved from the literature, from a UK-based RCT [personal communication - Dr Chris Rogers, 12th June 2013] and expert opinion. In addition, progression data on visual acuity were based on the two year follow-up MARINA study.[68] All these data were based on short follow-up but in a number of cases extrapolated to a lifetime time horizon. These clear limitations of the analysis indicate that its results should be interpreted with caution. Further research looking at the individual's nAMD active/inactive status is desirable. A conditional or a retrospective analysis of existing datasets would be helpful in order to obtain data to inform future economic models.

The analysis was conducted from the NHS and Personal Social Services perspective, incorporating cost of visual impairment that considered, for instance, cost for community care and residential care. The model, however, did not take into account the cost for patients or their carers. For instance, as this is likely to be an elderly population, someone might accompany the patient for their monitoring visits. These costs have not been considered in the model.

9.2.3 Uncertainties of the economic analysis

Undoubtedly, the limitations of the data together with the assembly of key data of varied quality are of most concern. Only two and three SD-OCT studies, respectively, contributed to the diagnosis and monitoring performance data in the economic model. Moreover, while OCT diagnosis and monitoring sensitivity and specificity data were retrieved from a systematic review of the literature, no such data were available for other tests proposed in alternative diagnosis or monitoring pathways, e.g. examination by the ophthalmologist or the monitoring assessment by a nurse or technician. Therefore, data for the model were obtained from expert opinion. These constitute major limitations of the analysis and further research in these areas is needed.

10 CONCLUSIONS

10.1 Implications for service provision

In terms of OCT test performance, the evidence, which was limited in quantity, especially for monitoring studies, and variable in quality, suggests that:

- For diagnosis of newly suspected nAMD, OCT has high sensitivity (median 94.5%) and moderate specificity (median 73.5).
- For monitoring of those previously diagnosed with nAMD, OCT has relatively high sensitivity (median 95%) but low specificity (median 48%)

The strategy that based its diagnostic decision on the results of FFA only, combined with a nurse or technician-led stepwise approach for monitoring, had the lowest expected total cost and a 47% probability of being cost-effective at a £30,000 threshold value of willingness to pay for an extra QALY. In addition, this strategy dominated all others apart from one (i.e. diagnosis with FFA combined with stepwise ophthalmologist-led monitoring) in the great majority of sensitivity analyses. The economic evaluation results suggest that strategies that used OCT test results alone to make diagnosis or monitoring treatment decisions were unlikely to be a cost-effective use of resources. This seems to be driven by the OCT low specificity inducing a high number of individuals with false positive test results being treated.

There has already been a shift in the diagnostic and monitoring pathways for nAMD caused by the adoption of OCT. At the diagnostic stage OCT is currently used in addition to FFA (reference standard), while for monitoring it has largely replaced FFA, which is only used in selected circumstances. The evidence suggests that using OCT as the only test for monitoring patients with nAMD and detecting activity would, potentially, result in a substantial proportion of patients receiving treatment unnecessarily with intraocular injections of anti-VEGF.

The continuing rise in the ageing population, with increasing numbers of people being diagnosed with nAMD and moving on to monitoring for renewed disease activity, will continue to present challenges for ophthalmology departments to have sufficient capacity to provide timely testing, and treatment.

10.2 Suggested research priorities

- Regarding monitoring of nAMD, in current practice OCT is routinely used, while FFA is used only in particular scenarios. There is a substantial disagreement between OCT and FFA. There is a need to research that OCT (without FFA) is an acceptable way of detecting

active nAMD and guiding treatment. As there is the theoretical possibility of OCT being better in some cases than the current reference standard, such studies might be designed to include a 'fair umpire' test, if available, to examine differences between OCT and FFA, or should be designed to incorporate a period of follow-up to assess the consequences of the tests in terms of clinical effectiveness outcomes (for example visual acuity). Currently used SD-OCT models should be evaluated, rather than TD-OCT.

- Regarding diagnosis of nAMD, current practice consists of FFA (as reference standard) associated with OCT. Further research should be considered to establish the added value of OCT, and whether OCT (associated with slit-lamp biomicroscopy and visual acuity) can fully replace FFA. As above, such studies might be designed to include a 'fair umpire' test, or the evaluation of the consequences of the diagnostic intervention. Currently used SD-OCT models should be evaluated, rather than TD-OCT.
- Regarding the different phenotypes of nAMD, further evidence on the natural history, efficacy of treatment and diagnostic performance of OCT according to phenotype of nAMD is required.
- For both diagnosis and monitoring of nAMD, prospective studies are required to assess the diagnostic accuracy and clinical effectiveness of strategies involving possible different combinations and sequences of tests (e.g. visual acuity, slit-lamp biomicroscopy, fundus autofluorescence imaging, OCT), including a comparison of their interpretation by ophthalmologists compared with other health professionals.
- To strengthen the evidence base used to develop the economic model, it would be important to explore the likelihood of active and inactive nAMD individuals becoming inactive or active, respectively. In addition, a preference based study to assess utility weights (e.g. decrements) associated with treatment and frequent monitoring is needed.
- Further research is needed to evaluate health status (utilities) in patients with nAMD, taking into consideration the visual function and spectrum of disease in both eyes and exploring the value added by inclusion of fellow eye information.

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